

# Research Rashomon

Lessons from the  
Cameroon Pre-exposure  
Prophylaxis Trial Site



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We hope that by documenting the complexity of this case study and suggesting lessons for future trials, this report can help strengthen the prevention research field moving forward.

**Rashomon** is a term from psychology that refers to the subjectivity of perception and recall, by which observers are able to produce substantially different but equally compelling accounts of an event. It is named for the 1950s Japanese film *Rashomon* directed by Akira Kurosawa, in which a crime witnessed by four individuals is described in four mutually contradictory ways.

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## Acronyms and abbreviations

<b>AIDS</b>	Acquired Immunodeficiency Syndrome	<b>IRESKO</b>	Institute de Recherches et des Etudes de Comportements (Institute for Research, Socio-economic Development and Communication)
<b>ANRS</b>	Agence Nationale de Recherches sur le Sida (National AIDS Research Agency)	<b>MTN</b>	Microbicides Trials Network
<b>APNSW</b>	Asian Pacific Network of Sex Workers	<b>NCHECR</b>	National Centre in HIV Epidemiology and Clinical Research
<b>ART</b>	antiretroviral therapy	<b>NGO</b>	nongovernmental organisation
<b>ARV</b>	antiretroviral	<b>NIH</b>	US National Institutes of Health
<b>AVAC</b>	AIDS Vaccine Advocacy Coalition	<b>PLWHA</b>	people living with HIV/AIDS
<b>AZT</b>	zidovudine (formerly azidothymidine)	<b>PMPA</b>	(R)-9-(2-phosphonylmethoxypropyl) adenine
<b>CAB</b>	community advisory board	<b>PrEP</b>	pre-exposure prophylaxis
<b>CD4</b>	cluster of differentiation 4	<b>REDS</b>	Réseau Ethique Droit et Santé (Network for Ethics, Laws, and Health)
<b>CDC</b>	US Centers for Disease Control and Prevention	<b>SIV</b>	simian immunodeficiency virus
<b>CHP</b>	Care and Health Programme	<b>STI</b>	sexually transmitted infection
<b>CNMC</b>	Le Conseil de L'Ordre des Médecins du Cameroun (Cameroon National Medical Council)	<b>TDF</b>	tenofovir disoproxil fumarate, Viread
<b>FDA</b>	US Food and Drug Administration	<b>UCSF</b>	University of California at San Francisco
<b>FHI</b>	Family Health International	<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>FTC</b>	emtricitabine, Emtriva	<b>UNSW</b>	University of New South Wales
<b>GCM</b>	Global Campaign for Microbicides	<b>USAID</b>	US Agency for International Development
<b>HIV</b>	human immunodeficiency virus	<b>VOICE</b>	Vaginal and Oral Interventions to Control the Epidemic
<b>IAS</b>	International AIDS Society		
<b>IAVI</b>	International AIDS Vaccine Initiative		
<b>iPrEX</b>	Pre-exposure Prophylaxis Initiative		
<b>IRB</b>	institutional review board		

# 1. Preventing prevention trial failures: What have we learned?

The use of existing antiretroviral (ARV) drugs to prevent HIV infection among uninfected individuals is an experimental strategy known as pre-exposure prophylaxis (PrEP). Although still unproven,

PrEP is considered a very promising new prevention approach. Unlike a microbicide or HIV vaccine, the drugs necessary for PrEP are widely in use, relatively well-understood, and already licenced and approved by regulators for treating AIDS. Human clinical trials of PrEP therefore emerged in the late-1990s as one of the most urgent priorities for the field of HIV prevention research.

Among existing antiretroviral drugs, oral tenofovir (tenofovir disoproxil fumarate, or TDF, marketed as Viread by Gilead Sciences) was and continues to be one of the most promising candidates for PrEP. Used alone or in combination with FTC (emtricitabine, or the brand name Emtriva), another marketed AIDS drug manufactured by Gilead, tenofovir has limited side effects, a strong safety profile, and remains active in the body for a long time. Moreover, tenofovir can be taken as a once-a-day pill and some studies suggest that resistance to tenofovir emerges more slowly than resistance to other antiviral drugs.

To determine whether tenofovir can be used for prevention, however, tenofovir and/or Truvada (a combination drug including tenofovir and FTC) needed to be tested in clinical trials among non-infected individuals at high risk of acquiring HIV. Several questions needed to be addressed: Are these drugs safe for long-term use among HIV-negative individuals? What is the likelihood that PrEP would promote the emergence of resistant strains of HIV? Will it work to prevent or reduce the likelihood of HIV acquisition? And what about side effects, costs, access, and ease of use?

By early 2004, six clinical trials were underway or being planned to test oral tenofovir for PrEP. The overall cost of the trials was estimated to be in the tens of millions of dollars US. These funds had to be raised from government and public-interest sources, since a PrEP drug for preventing the HIV epidemic in the world's poorest countries has not been viewed as a significant commercial opportunity by pharmaceutical companies.

Against this backdrop, two of the tenofovir PrEP trials were planned in West Africa (with sites in Cameroon, Ghana, and Nigeria) and in Cambodia. In 2002, Family Health International (FHI), a large not-for-profit,

nongovernmental, international health organisation, received a US\$6.5 million grant from the Bill & Melinda Gates Foundation to conduct a multi-country trial of oral tenofovir for PrEP in Cameroon, Ghana, and Nigeria, and one Asian site. That same year, the US National Institutes of Health (NIH) approved a grant to Dr. Kimberly Page Shafer of the University of California at San Francisco (UCSF) to conduct a trial of oral tenofovir as PrEP among sex workers in Cambodia. FHI had been requested by the Gates Foundation to fund the University of New South Wales (UNSW) to identify and oversee an Asian site. Dr. John Kaldor was the UNSW lead investigator, and he eventually decided to join with Dr. Shafer to work on the Cambodian study.<sup>1</sup>

Although the FHI study teams had internal discussions regarding possible study sites, relatively little external consultation occurred regarding the choice of countries for the West African trial. This issue was raised at a small informal ethics consultation on the proposed trials, sponsored by the Gates Foundation in 2001. Despite the important and groundbreaking nature of these trials, this meeting—attended primarily by researchers, ethicists, and advocates from the United States—was the only consultation sponsored before the Gates Foundation funded the trials.

In 2003, formative research began, with enrolment of women scheduled to begin at the West African trial sites in 2004. To the considerable surprise of researchers, advocates, and donors, the trials became embroiled in escalating controversies, sparked by protests by some AIDS activists. The activists not only raised questions about how the research was being conducted, but also challenged some of the fundamental ethics and underlying motives of the research. The researchers felt some of the questions and challenges were uninformed, and thought some of the attention-grabbing tactics the activists used—like spattering fake blood over the Gilead Sciences booth at the Bangkok AIDS conference in July 2004—were unwarranted and inflammatory.

Many of the issues the activists raised were legitimate—indeed, many of the same issues had been vetted and debated at the Gates-sponsored ethics consultation more than two years earlier, and some also had been

1. For more in-depth description and analysis of the Cambodia tenofovir PrEP trial, see Forbes A and Muldaliar S. *Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia*. Washington, DC: Global Campaign for Microbicides; 2009. Also see Page-Shafer K, Saphonn V, Sun L, Vun M, Cooper D, Kaldor J. HIV prevention research in a resource-limited setting: the experience of planning a trial in Cambodia. *Lancet*. 2005;366(9495):1499-1503.

raised by the multiple institutional review boards (IRBs) that had reviewed and approved the protocols. The specific triggering issues were somewhat different in Cameroon and Cambodia, where protests came from a union of sex workers rather than AIDS activists. However, what is perhaps most remarkable in retrospect was not the critique itself but the inability of stakeholders—all committed to ethical HIV prevention research—to deal with each other during the window of opportunity when dialogue may have been able to resolve some of the differences and allow the research to move forward. Eventually, a French television programme on France 2 picked up and magnified the controversy through sensationalised reporting. The report, aired in France, included misinformation which in turn was amplified and spread through postings on the Internet and in coverage in the Cameroonian media. The governments that had approved the trials were called to account by the media and the community. Not surprisingly, in less than a year, approvals for the trials in both Cameroon and Cambodia were suspended.

The closing of the PrEP trial site in Cameroon and the failure of the Cambodia trial to start meant that the fundamental question—Is oral tenofovir a potentially safe and effective new tool to prevent or reduce the likelihood of HIV acquisition?—could be only partially answered. The West African trial did successfully demonstrate that tenofovir is safe for regular use by HIV-negative people, but not enough HIV infections occurred to determine whether it is effective in reducing the likelihood of HIV acquisition. The question of whether tenofovir is effective in preventing or reducing the likelihood of HIV acquisition remains unanswered, although seven additional trials are now underway and/or being planned, with the first results expected in 2009 (see Tables 1–3).

For prevention research as a whole, the cost—both in terms of this lost opportunity and in financial terms—was substantial. Scarce funds for extremely expensive public-interest health research were wasted. Personal, organisational, and institutional reputations were tarnished. Some even questioned the credibility and legitimacy of research on new HIV prevention technologies itself. Acrimony developed among stakeholders in the AIDS community, all of whom share a deep commitment to stopping the epidemic and need each other's trust and support. A message was sent to prospective government partners that support for clinical trials could be controversial and may even be an invitation to political ruin. And perhaps most painfully, the research enterprise lost trust among communities and trial participants who had every historical reason to be sceptical about drug research and its benefits, but at the same time, urgently need new approaches to HIV prevention.

The controversy that emerged in Cameroon and Cambodia continues to influence donors, drug companies, researchers, government officials, and the public, who may hesitate before engaging in future HIV prevention research. And with some regularity, an undated video of the France 2 story resurfaces on the Internet, re-igniting concern that an “unethical trial” is taking place in Cameroon. Although safety data from the West African trial have been crucial to advancing PrEP research, the trial did not generate sufficient data to determine the efficacy of oral tenofovir in preventing HIV infection. Given this missed opportunity, what are the lessons for prevention trials that can help us do better next time?

This report looks at that question. Broadly speaking, the central message is unmistakable: In the laboratory perhaps, science can indulge its natural preferences for objectivity, political neutrality, and pristine research environments. But in the field of HIV prevention research, with its numerous sensitivities, that expectation is naïve and can invite failure. Researchers need to fully internalise that insufficient attention to political context, ethical issues, and public perception can halt a clinical trial as definitively and quickly as negative findings at a data safety and monitoring board review. This means that prevention researchers need to do more than nod to “social factors.” They need to think about human, social, and political issues actively and strategically at every step of the conceptualization, design, conduct, and follow-through of trials. This is especially true in resource-constrained countries where economic disparities and complex colonial histories are involved, and even more so when issues involving sex and gender are central.

Moving beyond the basics is not easy. Securing research funding, producing credible data, and negotiating peer review panels is hard enough without simultaneously introducing sociology, history, politics, and mass media management into research plans and budgets. Yet fairly or not, prevention trials seem to realistically require just that. This report explores the lessons and implications from the oral tenofovir PrEP trial Cameroon site to demonstrate why this is so. While it refers to the Cambodia trial in several places, that story—with its own lessons—is covered in more detail in *Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia*.

Any analysis based on just one example is necessarily limited in what it can represent. Many features of the Cameroon story indeed seem unique. In contrast to trials of experimental vaccines or microbicides, the tenofovir PrEP trials were designed to test an existing AIDS treatment drug that at the time was still not widely available globally. While Gilead Sciences

## Status of PrEP trials to date

**TABLE 1: Ongoing and planned PrEP trials as of July 2008**

Location	Sponsor/Funder	Population (mode of exposure)	Intervention arm	PrEP strategy(ies) being tested	Status/Expected completion
United States	CDC	400 gay men and other men who have sex with men (penile/rectal)	1	TDF	Fully enrolled – ongoing / 2009
Thailand	CDC	2,400 injecting drug users (parenteral)	1	TDF	Enrolling / 2009
Botswana	CDC	1,200 heterosexual men and women (penile and vaginal)	1	TDF+FTC (switched from TDF Q1 2007)	Enrolling / 2010
Ecuador, Peru, South Africa, United States, additional sites to be determined (iPrEX Study)	NIH, Gates Foundation	3,000 gay men and other men who have sex with men (penile/rectal)	1	TDF+FTC	Enrolling / 2010
Kenya, Uganda (Partners PrEP Study)	Gates Foundation	3,900 serodiscordant heterosexual couples (penile and vaginal)	2	TDF, TDF+FTC	Enrolling / 2012
Kenya, Malawi, South Africa, Tanzania (FEMPrEP)	FHI, USAID	3,900 high-risk women (vaginal)	1	TDF+FTC	Planning / 2012
Southern Africa, sites to be determined (VOICE Study)	MTN, NIH	4,200 sexually active women (vaginal)	3	TDF, TDF+FTC, TDF gel	Planning / 2012 Anticipated start Q1 2009

CDC, US Centers for Disease Control and Prevention; MTN, Microbicide Trials Network; NIH, US National Institutes of Health; USAID, US Agency for International Development

**TABLE 2: Completed PrEP trials**

Location	Sponsor/Funder	Population (mode of exposure)	Intervention arm	PreEP strategy being tested	Completion date	Key findings
Ghana*	FHI	936 women (vaginal)	1	TDF	2006	No statistically significant differences in rates of adverse events between women who received the study drug and those who received placebo during the trial. In addition, no evidence in this sample of women of complications such as hepatitis flares after the study drug (which is also a hepatitis treatment) was stopped. There were two infections amongst women taking the study drug compared to six amongst women receiving placebo. This is not a statistically significant finding and should not be interpreted as evidence that PrEP works. However, these safety data do provide a rationale for further study.

\*Analysis included some data gathered in Cameroon and Nigeria prior to closure of these trial sites.

**TABLE 3: PrEP trials halted or cancelled to date**

Location	Sponsor/Funder	Population (mode of exposure)	Reason for closing
Cambodia	NIH/FHI	960 women (vaginal)	Stopped before enrolment Controversy stemming from local and international activist groups' ethical concerns about standards of health care for volunteers during and after the trial
Cameroon	FHI	400 women (vaginal)	Stopped after enrolment Controversy related to international debate around trial ethics and standard of care that originated with Cambodian trial
Malawi	FHI	400 men (penile)	Stopped November 2005 before enrolling Concerns on the part of Malawi Ministry of Health that studies of tenofovir as PrEP could complicate use of the drug as a treatment for HIV-infected individuals
Nigeria	FHI	400 women (vaginal)	Stopped by trial sponsors due to concerns about local sites' capacity

Thanks to the AIDS Vaccine Advocacy Coalition for permission to include these tables. Current information on PrEP trials is available at [www.avac.org](http://www.avac.org).

was not actively engaged in conducting the PrEP trials, the trials were taking place at a unique point in time. International commitment to universal access was growing and a great deal of attention was being focused on finding ways to provide treatment drugs to people with AIDS. This provided activist protesters with a tactical opportunity to question Gilead about the PrEP trials and underscore the limited availability of tenofovir for treatment. In the course of ongoing work monitoring AIDS research being supported by the French government's national AIDS research agency (Agence Nationale de Recherches sur le Sida or ANRS), Act Up-Paris and REDS (Réseau Ethique Droit et Santé, the Network for Ethics, Laws, and Health), the two nongovernmental organisations (NGOs) most involved, came across the tenofovir PrEP trial during a visit to Cameroon. Act Up-Paris brought the trial to the attention of the France 2 programme. That programme reported sensationalist and, in some cases, unsubstantiated assertions that were difficult if not impossible for a research enterprise or the Cameroonian government to address. These circumstances came together in an exceptional way—a “perfect storm”—that overwhelmed the Cameroon trial site.<sup>2</sup>

Despite these exceptional circumstances, on balance, the Cameroon story shares many similarities with other transnational prevention trials underway or planned for the future, including the next wave of PrEP trials, ongoing vaccine trials, and microbicide efficacy trials. First, the tenofovir PrEP trials—like all HIV prevention research—deal with charged areas of sex, sexuality, and disease, and also may involve stigmatised people and behaviours. Second, international research is increasingly monitored not only by ethics review boards and regulatory agencies, but often by well-organised, passionate, activist networks committed to protecting the interests of trial participants and communities, among other concerns. Third, the array of new communications media—listservs, cell phone video, instant messaging, Internet telephony, and so forth—means that claims of exploitation or abuse, both real and rumoured, can travel around the world in a matter of hours, and may continue to echo and be amplified whether or not they are true. Finally, the Cameroon environment had many elements of high political risk—income disparities between researchers and participants, a legacy of distrust over drug trials in Africa, trial participants from vulnerable and stigmatised populations, and academic rivalries over who should lead HIV research in the country. Yet because of the need to evaluate HIV prevention products in populations where risk of HIV is high, settings like

Cameroon are precisely those where HIV prevention research needs to succeed.

In reconstructing the story of the Cameroon PrEP trial site and developing our analysis and recommendations, we reviewed numerous documents, including protocols, transcripts, reports, abstracts, correspondence, press releases, press coverage, published articles, and draft papers. We conducted interviews with many though not all of the key people and organisations involved. These interviews were conducted by telephone and in person, including during one trip to Cameroon and several visits with key individuals and organisations in Europe. The people interviewed included international and national researchers involved in the clinical and social science aspects of the trial, activists, communications specialists, civil society organisations, government officials, donors, and international organisations (see Annex 2 for a list of people interviewed). We want to note and thank the people we interviewed for their time and the frankness and spirit of reflection with which they offered their thoughts and perspectives.

The following chapters recast this story in four different lights. Chapter 2, which follows, lays out as objectively as possible the chronology of events in detail. It begins with a brief explanation of PrEP, the evolution of interest in tenofovir for HIV prevention, and the Gates Foundation's consideration of a multi-country research grant to test oral tenofovir in a Phase 2b clinical trial. Box 1 (“The tenofovir trial in Cameroon: key actors”) briefly introduces the key institutions that played a central role in the trial and the protests. Chapter 2 also summarises issues raised during a one-day ethical consultation hosted by the Gates Foundation in 2001. In hindsight, this consultation was important as the first of a series of significant missed opportunities. Stakeholders and experts at the consultation articulated, debated, and made recommendations on a number of potentially contentious issues. Many of these issues, including the choice of study population, the need to ensure access to treatment for seroconverters, and the lack of safety data among HIV-negative individuals, are precisely those that were central to the activists' critique. Regrettably, not all of these issues were addressed by the funders or researchers in planning and implementing the trial. This section also describes the planning and preparation for the trial; the design of both formative and clinical studies; the process of community consultation; the government's review and approval of the research; selection and initial recruitment of participants; and finally, the controversy and its aftermath.

The Cameroon tenofovir experience has no simple truth but rather many perspectives. Chapter 3 revisits

2. Forbes A and Muldaliar S. *Preventing Prevention Trial Failures: A Case Study and Lessons for Future Trials from the 2004 Tenofovir Trial in Cambodia*. Washington, DC: Global Campaign for Microbicides; 2009.



these events from the differing vantage points of those who were principally involved—the international and national PrEP researchers, the international and national activists and advocates, the government, the Cameroonian public, and the women who enrolled and participated in the trial. Chapter 3 illustrates that despite very different and at times opposing perspectives, most of the players were essentially on the same “side”—seeking to facilitate ethical research to address the urgent need for new HIV prevention options. Despite this shared goal, they could not find a way to move rapidly to share information, organise discussions, address each others’ concerns, and problem-solve to move the research forward.

Chapter 4 analyses the trial’s main problems and misunderstandings in five thematic areas. The first section looks at issues of **study design and process**. For example, it discusses key choices such as the selection of the study site, explaining how investigators had to balance practical and scientific considerations. It also makes clear why the activists questioned these decisions and could not obtain satisfactory answers to their questions and concerns.

This section also explores the critical issue of what constitutes meaningful community consultation and involvement, and who is empowered to decide on what. At the Cameroon trial site, FHI collected social and behavioural data to inform the conduct of the trial but did not have an explicit plan for community involvement. While the social science data informed aspects of the trial design and implementation, it did not translate into transparent consultation about the research, or a shared mechanism or process for joint problem-solving. As a research team, the social scientists felt an obligation to maintain the integrity of the formative research (allowing for systematic data analysis and participant confidentiality). Without a parallel process for community consultation, neither the process nor the outcome of the social science research as “consultation” was transparent. It seemed suspect to many of the activists when the researchers would not clearly point to results or people who had participated in the process.

The third section looks at the limitations of **existing norms and standards**. A broad array of internationally accepted policies and guidelines provide general ethical guidance for all clinical trials—the Nuremberg Code, the Declaration of Helsinki, the Council for International Organizations of Medical Sciences (CIOMS) guidelines, and so forth. Yet application in practice is seldom black and white, and it certainly was not in this case. For example, there is little consensus about the obligation of researchers to provide health

care to participants over the long term, or approaches to providing or ensuring informed consent. It is not surprising then that there are different views about how to implement this guidance in practice in order to conduct an “ethical” trial.

The fourth section, **research management**, considers the vast range of choices and pragmatic implications of who has (or should have) responsibility for what in a complex multi-site, international trial. The interviews conducted for this case study repeatedly circled back to fundamental questions of accountability and authority. Which stakeholders—the researchers, donors, ethical review boards, Ministry of Public Health, pharmaceutical company, community members, local advocates, journalists, and so on—should have been accountable for what happened, what did not happen, and what might have been foreseen?

The fifth section deals with the factor that most directly led to the suspension and eventual closure of the Cameroon trial site—**communication and language**. The scope of communication issues emerging from the interviews included a lack of communication, lack of purposeful communication, miscommunication and misrepresentation, and inadequate appreciation of the consequences of style and tone.

The sixth section illustrates the catalytic role that **activism** can play. While the activists have been blamed for closing down the trial, and their tactics were at times sensationalist and charges not always substantiated, they raised many fair questions that deserved to be answered. They report that they repeatedly approached the researchers in Cameroon for responses and actions to address the concerns they had raised, and that six months passed between the time they first learned about the trial and when they took their concerns to the media. Their confrontational style made dialogue harder. However, a culture of information-sharing and mechanisms for a timely and productive dialogue were not in place. What is clear is that civil society organisations, including activists, increasingly see themselves as key players with a stake in trials and that researchers need to involve them from the outset. For their part, activists and advocates need to hold themselves and each other to standards of evidence for their claims and challenge inflammatory tactics.

The conclusion of this report, Chapter 5, translates the preceding analysis into concrete lessons for moving forward. We hesitate, though, to frame these conclusions as “recommendations.” Instead, we have termed them “requirements,” because we believe as a practical matter that they describe necessary minimal characteristics for successful prevention trials. The

experience in the Cameroon site of the West African PrEP trial—as well as a great deal of other collective experience—persuades us that trials that do not meet

these requirements—in operation, not just on paper—are not likely to succeed.

## 2. The story of the Cameroon PrEP trial

### Chemical prophylaxis in the fight against HIV/AIDS

The first use of antiretroviral drugs for HIV prevention came soon after the approval of the first HIV therapy drug, AZT (zidovudine, formerly azidothymidine), in 1987. Physicians began administering AZT to health care providers exposed to blood or body fluids likely to be infected with HIV.<sup>3</sup> Studies later showed that this practice, known as post-exposure prophylaxis, reduced the risk of infection by almost 80 percent.<sup>4</sup> The use of chemical prophylaxis to prevent HIV infection expanded in 1994, when it was found that AZT used before, during, and after childbirth could reduce the risk of transmission of HIV from mother to child by two-thirds.<sup>5</sup> This finding, considered by some to be “the most stunning and important result in clinical acquired immunodeficiency syndrome research to date,” underscored the importance of continued research into pre-exposure prophylaxis (PrEP).<sup>6</sup>

### Evolution of interest in tenofovir

As far back as 1995, when tenofovir was still under development and known as PMPA [(R)-9-(2-phosphomethoxypropyl)adenine], it was tested in macaque monkeys to determine its effectiveness in preventing transmission of the simian immunodeficiency virus (SIV), which is closely related to HIV. During these initial vaginal challenge tests, PMPA prevented SIV infection in 100 percent of macaques that received it, whereas all the control macaques became infected. At the time, the researchers noted that “these results suggest a potential role for PMPA prophylaxis against early HIV infection in cases of known exposure.”<sup>7</sup> PMPA also was being formulated as a gel and tested as a potential vaginal microbicide.<sup>8</sup>

In the 1990s, antiretroviral drugs began to improve, becoming easier to take, better tolerated, and having

fewer side effects. They also were becoming less expensive and less likely to produce resistance. As this occurred researchers and others began to enthusiastically support the notion of testing ARVs as potential prophylactics for high-risk populations. These products existed, had been shown to be safe among HIV-positive individuals, and were already approved for use by regulatory authorities. Therefore, if shown to be effective for preventing HIV infection, they could be made available more quickly than other biomedical approaches being tested.

Because an HIV prevention drug must be taken consistently by healthy people over a long period of time, several qualities are particularly important—long-term safety, the likelihood of developing resistance, side effects, ease of use, and cost. Tenofovir was considered to be among the strongest candidates for testing because it had a reasonably good safety profile in HIV-positive people, and some studies suggest that resistance to HIV appeared to emerge more slowly than with other antiretroviral drugs. As a once-a-day pill, the tenofovir PrEP regimen would be relatively easy to use. However, tenofovir was still expensive and not widely available, and not yet approved by regulatory authorities in many countries even for treatment. So it was not clear how accessible or affordable it would be.

### The development of the tenofovir PrEP trials, late 2001

Tenofovir was first approved by the US Food and Drug Administration (FDA) as an AIDS treatment drug in October 2001. Almost immediately, researchers started contemplating the use of tenofovir as a potential drug for HIV prevention. Family Health International (FHI), a US-based international nonprofit public health agency, submitted a proposal to the Bill & Melinda Gates Foundation to evaluate the use

3. US Centers for Disease Control and Prevention. Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood—France, United Kingdom, and United States, January 1988–August 1994. *Morbidity and Mortality Weekly Report*. 1995;44(50):929–933. Available at [www.cdc.gov/mmwr/preview/mmwrhtml/00039830.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/00039830.htm). Accessed August 7, 2006.

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5. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine*. 1994;331(18):1173–1180.

6. Pizzo PA, Wilfert CM. Perspectives on paediatric Human Immunodeficiency Virus infections. *Paediatric Infectious Disease Journal*. 1995;14:536. In: White E. *Breastfeeding and HIV/AIDS: The Research, The Politics, The Women's Responses*. Jefferson, NC: McFarland; 1999.

7. Tsai CC, Follis KE, Sabo A, Beck TW, Grant RG, Bischofberger N, Benveniste RE, Black R. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. *Science*. 1995;270(5239):1197–1199.

8. For a good summary of animal studies, see Kresge KJ. Treatment as prevention: researchers are studying the use of licenced antiretrovirals to prevent—rather than treat—HIV infection. *IAVI Report*. 2006;10(3):1.

## The tenofovir trial in Cameroon: key actors

**Act Up-Paris:** Act Up-Paris, an activist association, was founded at the Gay Pride March in Paris in June 1989 to transform its members' anger about the AIDS epidemic into a political response. They fight for the rights of all people with HIV and AIDS, for sexual freedom, and to give voice to those who are traditionally exploited and silenced. While they are particularly known for their attention-grabbing and media-savvy protest actions, known as "zaps," used to shame decision-makers into action, they also lobby and negotiate with government, pharmaceutical companies, and medical and research institutions.

**Care and Health Programme (CHP):** CHP is a nongovernmental organisation (NGO) created in 1996 by former Cameroonian employees of Family Health International (FHI)/AIDS Control and Prevention Project to carry on activities related to AIDS and sexually transmitted infections (STIs), following on FHI's commitment to building local research capacity with local ownership. CHP is committed to reducing the spread of HIV infection in Cameroon through a range of projects, including conducting training, providing education, researching behaviour change communication, building NGO capacity, and providing technical assistance for STI and HIV research. CHP has provided HIV education to high-risk groups, such as military personnel, sex workers, university students, and young people not attending school.

**Family Health International:** FHI is a not-for-profit, international public health agency founded in 1971 that has worked in more than 100 countries. Initially focused on contraception and family planning, HIV and AIDS has formed a key part of FHI's work and mission since 1986. Among other work in the field, FHI has served as the operations centre for consecutive US National Institutes

of Health awards to build capacity and conduct multi-site, international HIV prevention trials: HIVNET (1993), the HIV Prevention Trials Network (1999, 2006), and the Microbicide Trials Network (2006).

**Institute de Recherches et des Etudes de Comportements (Institute for Research, Socio-economic Development and Communication or IRESCO):** IRESCO, an NGO, is a Cameroonian research institute based in Yaoundé. It conducts research and manages programmes and projects to promote better health and quality of life, particularly for low-income and vulnerable populations. IRESCO's main areas of intervention are health, environment, and education, including water, malaria, HIV and AIDS, and family planning. IRESCO produces and disseminates study results and evaluations of development activities undertaken throughout Africa and has produced reproductive health and educational materials for young people.

**Réseau Ethique Droit et Santé (Network for Ethics, Laws, and Health or REDS):** REDS is an activist group established in Cameroon in 1998 and registered in 2000 to promote and protect the rights of people who are infected with HIV or affected by the AIDS epidemic. In the early 1990s, one of the founders was employed at SidAlerte, where he worked with a woman who had seroconverted during the Col-1492 trial. This prompted him to look at research and research ethics more closely and to launch REDS. REDS is the Cameroonian branch of the African Network on AIDS Ethics and Rights (Réseau Africain sur l'Éthique, le Droit et le VIH), funded through the United Nations Development Programme in Dakar. REDS seeks to ensure that research being conducted, particularly on people living with HIV/AIDS, is legitimate. REDS has both individual and organisational members.

of tenofovir as an oral prophylaxis to prevent HIV acquisition among high-risk populations. The proposed study was a randomised, double-blinded, placebo-controlled trial in uninfected women at risk for acquiring HIV in West Africa.

At about the same time, Dr. John Kaldor from the University of New South Wales (UNSW) in Australia was also developing a protocol to test oral tenofovir for PrEP. Dr. Kimberly Page Shafer, a researcher at the University of California at San Francisco (UCSF), had sent a similar proposal to the US National Institutes of Health (NIH) to test oral tenofovir as an HIV prevention method among sex workers in Cambodia.

For its part, Gilead Sciences, the company that developed tenofovir, was initially somewhat reluctant

to become involved with the prevention trials; it was already working to address registration, pricing, and access issues for treatment, and did not see the potential market for prevention being especially profitable. Gilead, however, has generally been supportive of PrEP research and has cooperated with the PrEP research field.

### Ethical consultation, November 2001

In November 2001, the Gates Foundation convened a one-day consultation of experts to consider ethical issues related to PrEP in general and a specific proposal put forward by FHI (see Annex 3 for a list of participants). A number of key concerns raised during the consultation were later echoed and amplified

by the activists, and ultimately contributed to the controversies that led to the trial closures in both Cambodia and Cameroon. These included questions about access to treatment for seroconverters; lack of safety data in healthy, HIV-negative people; choice of study population; and uncertainty about the distribution of the burdens and benefits of research.

These concerns were embedded in a far-ranging discussion during the ethics consultation. Among the issues raised were:

- **Balancing urgency with safety.** Participants discussed the importance of balancing the urgent need for alternative prevention methods, particularly female-controlled methods, with other concerns, such as the lack of safety data in HIV-negative people. While safety data on tenofovir as a therapy were available from HIV-positive individuals and were encouraging, no data existed specifically on the safety of the drug for use among non-HIV-infected individuals.
- **Choice and form of drug.** Questions were raised about whether oral tenofovir was the best choice to test for prevention. Concerns included whether the biological plausibility of tenofovir as an HIV preventive therapy was convincing; whether oral tenofovir was preferable to a gel formulation that was being developed for vaginal use; and the possible consequences of using an AIDS treatment drug for prevention. A related set of concerns centred on access to the drug: whether using tenofovir for prevention would be cost-effective; whether tenofovir would be accessible, particularly to the poorest and most vulnerable, if it were shown to be effective; and whether Gilead Sciences, which produced tenofovir, would be willing to lower the cost and/or waive patent rights in developing countries to make it more accessible.
- **Choice of country and trial population.** Participants raised a number of concerns regarding the proposed location of the trial (Cameroon) and the trial population (women with multiple sex partners, including but not limited to sex workers). They questioned whether it was appropriate to conduct the trial with a vulnerable population of women in a developing country if it could potentially be done in a less vulnerable US or European population; this was felt to be a particular problem if the product were found to be effective and the United States would be a main market.
- **Access to care and treatment for seroconverters.** Other major issues included conducting the trial in a country without a voluntary counselling and testing programme, and evaluating the use of an HIV

treatment drug for prevention in a country where antiretroviral therapy (ART) was not yet available to people living with HIV/AIDS (PLWHA). At the time, few people in Africa had access to antiretroviral therapy and efforts to meet universal access to antiretroviral therapy were still nascent.

- **Benefits to participants and the country after the trial.** The consultation also raised the issue of what benefits the participants would receive after the trial was completed, particularly whether they would have access to tenofovir if it were shown to be effective. The consultation report noted that it would be important to specify what entity (for example, the national government, Gilead Sciences, and/or the Gates Foundation) would be responsible for providing the drug to trial participants and in other developing-country settings and their level of commitment to doing so.

The consultation concluded that:

- Proceeding with a Phase 3 efficacy trial of oral tenofovir for prevention before doing Phase 2 safety trials in HIV-negative persons was not appropriate.
- Human safety trials of tenofovir in HIV-negative populations in the United States was appropriate and could be followed by efficacy studies in high-risk US populations and in similar populations in other countries. Ultimately, PrEP testing should involve a well-funded programme of multiple trials to evaluate the method among different users in different settings. This would ensure that the burdens and benefits of research were shared.
- The issues of access to HIV counselling and testing, and to antiretroviral therapy, could be addressed by conducting Phase 3 trials in developing-country settings where such access either already existed or was being established, such as Botswana, Brazil, and/or Thailand. Participants considered it extremely problematic to test an antiretroviral for prevention in settings where antiretroviral drugs for treatment were not generally available.
- Attention should be given to developing trial sites that would allow for testing vaginal tenofovir when Phase 1/2 studies were completed, if the results warranted such trials. Vaginal tenofovir offered certain advantages over oral tenofovir: as a topical drug, it would be less likely to be absorbed systemically, which would reduce safety issues and the likelihood of encouraging resistance; and since it could not serve as a treatment, it was less likely to be appropriated by male partners or “shared” with family members who were sick and in need of HIV treatment.

## Response to ethical concerns, 2002

Following the consultation, FHI considered various options, including redirecting the bulk of the research to US populations, followed by Phase 2 safety trials in one or more developing-country settings. Repeating the safety trials would ensure that the safety profile of the drug was not affected by conditions endemic to those settings, such as malaria or nutritional deficiencies. The Gates Foundation agreed to consider funding Phase 2 safety trials in developing countries, but another donor would need to be found to fund trials in the United States. After participating in the consultation, the US Centers for Disease Control and Prevention (CDC) started a process to support a Phase 2 safety trial in the United States among men who have sex with men; the trial started in 2005. The CDC also has organised effectiveness trials in Thailand and Botswana.

At this point, FHI felt the need to “step back from the specific concerns raised during the ethics consultation and consider the broader questions [underlying them].”<sup>9</sup> FHI defined four main ethical questions:

1. Are the trials addressing a significant health risk that is a priority for the countries that will be hosting the research?
2. Will the host-country populations benefit from the research results?
3. Can appropriate steps be taken to minimise all medical, social, and psychological risks associated with the research?
4. Is the research unnecessarily burdening vulnerable populations?

To address these issues, FHI proposed to:

- Make country site selection contingent on ensuring that national ministries of health would support the use of tenofovir for prevention should it prove effective and that the trial would not detract from the conduct of other important research or public health activities.
- Negotiate prior agreements between the host country and the Gates Foundation, Gilead, and any other potential sources of support, for implementation of an HIV chemoprophylaxis programme, if efficacy were demonstrated.

- Conduct formative research at all sites to identify effective strategies for an appropriate and effective informed consent process; risk reduction counselling; referrals for care for those identified as HIV infected; supporting sustainable improvements in local access to care; preventing inappropriate use of the study drug outside of the trial; and minimising the potential for stigmatisation of trial participants.
- Address safety issues by phasing the study with initial slow enrolment followed by appropriate medical monitoring throughout the trial and clear procedures for handling adverse medical events.

In terms of placing the burden on vulnerable populations, FHI noted that it would be impossible to conduct useful HIV prevention research with populations that were not vulnerable in some way, whether in the United States or elsewhere. They reasoned that, if the research were valuable and the potential benefits could be assured, the primary ethical issue was to minimise harm. They proposed to minimise harm by making every effort to identify populations that had strengths as well as vulnerabilities and to implement the research in ways that potentially enhanced strengths; by engaging in a process of community consultation through the formative research, with the goals outlined in the previous paragraph; and by making every effort to ensure that the trial would result in data of sufficiently high quality to guide public health decisions in the host countries and generate funding to support those decisions.

Based on this analysis, FHI proposed to conduct a Phase 2b pivotal trial, that is, a well-controlled trial to rigorously evaluate safety and efficacy. FHI argued that a study exclusively focused on safety in a developing country “potentially placed a significant level of risk on the most vulnerable participants with no guarantee that the research needed to determine efficacy would, in fact, take place.”<sup>10</sup> The trial was planned for three African sites and one Asian site, and included formative social science and behavioural science research.<sup>11</sup> Of note, the final proposal submitted to the Gates Foundation maintained the formative research objectives but dropped explicit mention of a community advisory board.

9. In an email from Kate MacQueen, Ward Cates, and Ronald Roddy (December 2, 2002): *Follow-up on Nov 2001 Gates Foundation ethics consultation on tenofovir DF*.

10. In an email from Kate MacQueen, Ward Cates, and Ronald Roddy (December 2, 2002): *Follow-up on Nov 2001 Gates Foundation ethics consultation on tenofovir DF*.

11. The Asian site was added at the Gates Foundation's recommendation, along with the proposal that FHI work on it with the team at the University of New South Wales. The idea of testing tenofovir as a potential PrEP had been discussed at the National Centre in HIV Epidemiology and Clinical Research (NCHECR) at UNSW after its director had heard about the results of the macaque study published by Tsai et al. in *Science* in 1995 during a meeting with Gilead. In mid-2001, at a conference in Australia, the NCHECR discussed the possibility of conducting a PrEP trial with Helene Gayle from the Gates Foundation, who encouraged them to put together a proposal. She then told them that she had received a similar proposal from FHI and proposed that the two groups work together. However, the “arranged marriage” between FHI and UNSW proved unworkable. Ultimately, the UNSW group joined with UCSF/NIH to conduct a trial in Cambodia, and FHI served mainly as a conduit of funds from the Gates Foundation to UNSW.

## Gates Foundation grant for clinical trials, October 2002

In October 2002, one year after the initial PrEP proposal had been raised with them, the Gates Foundation awarded FHI a US\$6.5 million, three-year grant for a multinational clinical trial to evaluate the safety and efficacy of tenofovir as a method of HIV prevention. After FHI received the grant, they developed the protocols for the formative research and the clinical trial, identified collaborating sites and partners, and obtained IRB and other clearances and approvals.

The research sites selected in Africa were in Cameroon, Ghana, and Nigeria. FHI had initially proposed a site in Cameroon in part because they had previously

conducted several clinical trials there and thus had a long, well-established collaboration with Cameroonian researchers whom they knew could conduct registration-level trials that would pass US Food and Drug Administration audits. The ethics consultation advised FHI to conduct the trial in more than one country to increase the generalisability of the data and to ensure that they would be able to recruit the number of women needed.

FHI met with the national health ministries and required that they agree to a “good faith effort” to support the inclusion of tenofovir for PrEP as a part of the national HIV prevention programme if it proved effective. The ministries were not required to commit to providing the drug or to define to whom it would be provided or how.

### Access to tenofovir

When the PrEP trial was being conducted, tenofovir was not registered in Cameroon, but some effort was made to work toward ensuring access in Cameroon and other low-resource settings. At the time, the Gates Foundation contracts included a relatively general statement that obliged grantees to conduct project activities in a manner that would further the foundation’s charitable goals.<sup>12</sup> In September 2002, the Gates Foundation, FHI, and Gilead Sciences agreed that Gilead would develop a global access plan if the prevention trials were successful. A few months later, in December 2002, Gilead announced its Global Access Program for tenofovir, in which it would make tenofovir available in 68 developing countries, including all African countries, at a preferential, no-profit price. In March 2005, the number of countries was increased to 97.

However, some people have been sceptical about Gilead’s commitment to access since the company has not been a leader in the area of preferential pricing and drug access. Gilead has been relatively slow to register tenofovir in the countries covered by its access programme. Some of

this delay can be attributed to the enormously complex, expensive, and diverse requirements of the myriad drug registration agencies in such a wide array of countries. As of June 2007, tenofovir was registered in only 25 of the 97 countries; Gilead submitted the regulatory dossier in Cameroon only in August 2008, and as of October 2008, the review was still pending.<sup>13</sup>

While the agreements to ensure post-trial access in Cameroon were a step in the right direction, none of the agreements or statements were specific about who would be provided access, which entity would be responsible for assuring access, or how such responsibility would be enforced.

In June 2007, the preferential price for tenofovir to treat AIDS was US\$17 per month (US\$204/year).<sup>14,15</sup> Even at this significantly reduced cost, it would be far out of reach in Cameroon, where per capita expenditure on ALL health services and products was US\$68 in 2002.<sup>16</sup>

BOX 2

12. In 2004, the Gates Foundation developed a policy included in grant awards that “Appropriate global health solutions must be made accessible (price, supply, and availability) to people most in need in developing countries.”

13. Available at [www.gilead.com/pdf/GAP\\_Registration\\_Status.pdf](http://www.gilead.com/pdf/GAP_Registration_Status.pdf). Accessed October 20, 2008.

14. Although this is an “at-cost” price, Médecins sans Frontières (Doctors Without Borders) reports that it will increase the cost of treating a patient for a year by four to six times. As demand and production increase, the price should go down.

15. Médecins sans Frontières. *Untangling the Web of Price Reductions: A Pricing Guide for the Purchase of ARVs for Developing Countries, 10th edition*. Geneva, CH: Campaign for Access to Essential Medicines; 2007. Available at [www.accessmed-msf.org/documents/Untangling10.pdf](http://www.accessmed-msf.org/documents/Untangling10.pdf). Accessed August 5, 2007. Price available at [www.gilead.com/gap\\_pricing](http://www.gilead.com/gap_pricing). Accessed August 5, 2007.

16. World Health Organization. *The World Health Report 2005: Make Every Mother and Child Count*. Geneva, CH: World Health Organization; 2005. Available at [www.who.int/whr/2005/annex/indicators\\_country\\_a-f.pdf](http://www.who.int/whr/2005/annex/indicators_country_a-f.pdf). Accessed January 15, 2007.

In December 2002, Gilead Sciences also agreed that if tenofovir proved effective for prevention, they would provide the drug free to participants in the placebo arm of the trial for one year, the length of the trial. In addition, they agreed that the ministries of health could purchase tenofovir for prevention at the preferential “access” price they had established for developing countries wishing to use tenofovir for HIV therapy (see Box 2, “Access to tenofovir”).

### **Design of formative and clinical studies, 2002–2003**

FHI intentionally planned and designed separate formative and clinical research studies in order to maintain the independence and integrity of the two research processes. They wanted to minimise the extent to which informants in the social and behavioural research would say what they thought the researchers wanted to hear if they associated the social science researchers with the clinical trial. In identifying their Cameroonian partners, FHI turned to organisations and researchers they had worked with before. For the formative research, they engaged the Institute de Recherches et des Etudes de Comportements (Institute for Research, Socio-economic Development and Communication or IRESCO), and for the clinical trial, Professor Anderson Sama Doh of the Faculty of Medicine and Biomedical Sciences at the University of Yaoundé, and the Care and Health Programme (CHP).

### **Minister of Public Health authorises the trial, January 2003**

As with many clinical trials, the protocol and other materials underwent multiple reviews. FHI obtained administrative authorisation for the clinical trial from the Cameroon Ministry of Public Health on January 23, 2003, and IRB approval from the National Ethics Committee of Cameroon on December 16, 2003. The IRB approval was accompanied by a letter that stated that the documents submitted responded to the concerns the committee had expressed in previous correspondence. Permission to conduct the trial in Douala was obtained from the Littoral Provincial Delegation of the Ministry of Public Health on April 22, 2004. The National Ethics Committee of Cameroon renewed its approval of the study on December 11, 2004. FHI’s IRB, the Protection of Human Subjects Committee, initially approved the study in August 2003, and this approval was renewed annually thereafter.

### **Formative research begins in Douala, September 2003**

The overall purposes of the formative research were to facilitate the implementation of the clinical trial and to translate the research results into prevention programmes if the intervention proved effective.

It had three primary objectives:

1. **Site preparation assessment:** to prepare the site for implementation of the clinical trial.
2. **Acceptability assessment:** to assess the acceptability of tenofovir as an HIV preventive intervention among the potential trial participants and their partners, potential users, providers, and community stakeholders.
3. **Research outcomes assessment:** to identify facilitators and barriers to the translation of the trial results for use in HIV prevention programmes.

It sought to identify and integrate context-specific factors that might vary from site to site with the trial factors that had to remain constant across the sites in West Africa and Asia so that data could be combined and results generalised.

Overall, the formative research team planned to conduct a minimum of nine focus groups and 120–200 in-depth interviews at each site (some interviewees would be interviewed more than once). The study participants included HIV-negative women and men at high risk for infection, their sexual partners, HIV prevention and care providers, community gatekeepers, the clinical trial staff, and local experts. The formative research team started data collection for the site preparation assessment phase in September 2003, in parallel with planning and preparation for the clinical trial. The acceptability assessment and the research outcomes assessment components were conducted concurrent with the clinical trial.

### **Site preparation assessment, September 2003**

The site preparation assessment included five components:

1. Identifying areas with high HIV transmission and assessing the community cohesiveness of the target population.
2. Assessing community consultation options.
3. Assessing informed consent process approaches to ensure that the terms used in the informed consent booklets were appropriate in the local language; to identify appropriate communications strategies for explaining complex concepts in the consent



form, such as the use of a placebo; and to explore strategies for evaluating participant comprehension.

4. Verifying whether FHI's assumptions about treatment and care were compatible with the values held by the community stakeholders;<sup>17</sup> identifying available resources for HIV care and potential referral sites for participants and their families; and getting community input on how to address broader access to care issues.
5. Assessing the extent to which stigma is a concern and its potential consequences, and developing strategies to reduce the risk of stigmatization and monitor for social harms during the trial.

The process also assessed HIV risk behaviours, existing prevention programmes, and unmet HIV prevention needs to inform the guidelines for HIV risk reduction counselling.

“Community” in this case was defined as people associated with the “high transmission areas” in Douala, where the research would take place. It included potential trial participants and partners of potential trial participants, as well as local HIV prevention and care providers and community gatekeepers. Significantly, it did not include other “communities”—national groups or individuals that might also have held interest in the research beyond the trial community.

Beginning in late September 2003, FHI first held expert meetings with community members and professionals familiar with HIV and at-risk populations. It combined this anecdotal information with epidemiologic information to identify potential high transmission areas. The formative research team then investigated a total of 25 sites in six high transmission areas. They conducted 53 in-depth interviews and five focus groups with women at high risk for HIV; community members; people living with HIV; health care providers; public health officials; and NGOs working on women's issues, HIV, or both. They also undertook onsite participant observations to find out more about the community, health beliefs, knowledge of HIV/AIDS, attitudes toward prevention research, level of understanding of and past experience with research, and to confirm information from the expert meetings.<sup>18</sup> The informed consent booklet concepts and text were tested in French and English. Data collection for this initial phase of the formative research was completed in February

2004 in Cameroon. In keeping with research practice, the key informants and focus group participants were guaranteed confidentiality. This means that the names of the individuals and groups that participated in this consultative process have not been made public.

### Sharing results of formative research, early-mid 2003

The results of the formative research were shared with the clinical research team. FHI intended to keep the in-country formative and clinical research teams distinct to reduce any bias in the information collected from participants, but to have them work together closely, with synergy and mutual influence. However, the extent to which this actually happened varied across the West African sites. Formative research findings did influence some of the strategies and approaches used for recruitment, retention, and referrals. During the time that questions and concerns were raised about the trial, the results of the formative research were still being formally analysed and so were not shared outside the research team.

### Act Up-Paris goes to Cameroon, May-June 2004

In May-June of 2004, two activists from Act Up-Paris, Fabrice Pilorgé and Régis Samba-Kounzi, travelled to Cameroon for three weeks to do research for the second issue of Protocol Sud, an Act Up-Paris newsletter about clinical trials in the global South. They had decided to focus the second issue on Cameroon because Act Up-Paris had a relationship with a group there, the Réseau Ethique Droit et Santé (REDS, Network for Ethics, Laws, and Health), and the Agence Nationale de Recherches sur le Sida (ANRS, the French National AIDS Research Agency) had on-going trials in the country. They knew about several trials in Cameroon, which they planned to investigate, but were not aware of the plans for the tenofovir PrEP trial at the time.

In Cameroon, the two French activists met with two members of REDS, Jean-Marie Talom and Calice Talom, who told them that they had heard about a trial in Douala. After a couple of visits to the trial site, which was still under construction, they were given the protocol for the clinical trial and the English-

17. These assumptions were that HIV prevention is as much a priority as treatment in the community; that HIV prevention research need not be tied to progress on the provision of treatment in the community; and that obstacles to treatment increase the importance of identifying effective prevention options. Based on this, FHI understood that its ethical obligation for providing HIV care was to facilitate access to the best possible care in the local setting and to assume appropriate care for any trial-related adverse events. They also intended to seek resources to support sustainable improvements in local access to prevention and care wherever feasible.

18. Nyiama TA, Mack N, MacQueen KM, Guest G, Namey E. *Addressing HIV prevention trial challenges through socio-behavioural research: Cameroon's tenofovir trial*. Poster presented at the XVI International AIDS Conference in Toronto, Ontario; 2006.

language informed consent booklets for screening and enrolment. It was at that point that Act Up-Paris learned that it was a PrEP trial assessing tenofovir. Unfamiliar with prevention research in general and PrEP trials specifically, Fabrice Pilorgé sought the opinions of an Act Up colleague in Paris with greater research expertise.

Together the four activists read the protocol and noted their questions and criticisms, after which they went to talk with Professor Doh, the coordinating investigator, and then with Alexis Boupda from CHP. Among others, they raised the following issues:

- The need to include female condoms in the prevention package.
- Whether the informed consent booklets would be translated into French.
- The need to provide antiretroviral therapy and psychological care for seroconverters and those who test HIV positive at screening.<sup>19</sup>

During their discussions, the researchers informed them that the booklets were being translated and that they were establishing an agreement with a hospital to provide antiretroviral therapy to seroconverters. In addition, the researchers reportedly indicated that the issues the activists had raised were pertinent and they would raise them with those who were responsible. The activists remained concerned, however, because their understanding was that the trial was scheduled to begin in 15 days. The activists noted that they were “pushy” and that some of their discussions with the researchers turned confrontational in tone.

Act Up-Paris and REDS then discussed the trial with the head of the national ethics committee; the Division de la Recherche Opérationnelle de Santé (Health Operations Research Division), which was new at the time; the Red Cross, which was working with sex workers; the Cameroon Network of People with HIV; Médecins Sans Frontières (MSF, or Doctors Without Borders); and various women’s associations.

The Cameroonian researchers report that they discussed with FHI the issues raised by the activists but found that the FHI researchers were reluctant to consider changes to the protocol. Protocols for multi-site trials, especially drug registration-level trials, can be inflexible given the need for comparable data across sites and the restrictions of Good Clinical Practice. In addition, the process for amending protocols is complex and time-consuming, requiring review by ethical review boards

and approval by international and in-country regulatory authorities that could take many months. This means that researchers try to minimise changes, and often combine changes into one amendment.

At the time of the study, the female condom was rare if available at all in Cameroon. The female condom was not part of the standard prevention package in other similar trials, and the researchers generally believed that, at the time, women were not interested in using the female condom. The Cameroonian researchers reported that FHI was not keen to add it: FHI argued at the time that no direct evidence had demonstrated the effectiveness of female condoms in preventing HIV, and because the trial was multi-centre, it would mean adding it at all the sites. The Cameroonian researchers did not insist. Regarding seroconverters, FHI was preparing a major protocol revision that would have included a study that would enrol trial participants who became HIV positive. These women would be followed for one year to monitor their CD4 counts and viral load to study resistance and disease progression. Women with chronic hepatitis B infection also would be monitored to determine whether, if tenofovir suppressed hepatitis B, they might be at risk of reactivation, or “flares,” when they were taken off tenofovir.<sup>20</sup>

## The clinical trial enrolment begins, July 2004

The trial enrolled HIV-negative women aged 18 to 35 who were at high risk of becoming infected with HIV. High risk was defined as being sexually active, with on average three instances of sexual intercourse per week, and also having had more than three sexual partners in the past month. The researchers did not label the trial participants as sex workers, although they recognised that some of the women defined themselves as such and many of them were engaging in transactional sex. Screening for enrolment in the clinical trial began in July 2004. By December, the trial was fully enrolled with 400 participants.

Recruitment in Cameroon was conducted through street outreach in areas that had been identified by the formative research team. The formative research team was known in the areas and served as a “bridge” to help familiarise and introduce the recruiters to the areas. Recruiters were paid a salary and were not compensated based on the number of participants referred or enrolled. To improve retention, recruiters followed up with participants and encouraged them to remain

19. In particular, the activists wanted to know if the researchers had an agreement with a hospital or organisation to provide ARVs and/or agreements with organisations of PLWHA to provide support.

20. This trial found no evidence of such “flares,” but it is being examined in ongoing PrEP trials.

enrolled in the study. They received a salary bonus if the participants they recruited stayed in the study.

## The study moves forward, July–December 2004

**Informed consent.** To obtain informed consent for screening and then for enrolment, the counsellors read each section of the relevant booklet aloud, explaining and answering any questions. The consent form was available in both English and French. Local translators sometimes used pidgin English or a native dialect for participants who were not able to speak either French or English. In addition to asking questions after each section, the counsellor asked a series of questions to check comprehension after the entire form was reviewed. When any question was not answered correctly, the section of the consent form was reviewed again. If the counsellor did not think the volunteer understood, she would not be enrolled in the study. If the woman agreed to be in the study, she signed the form.

Initially, all the participants had to be literate to enrol in the trial because they needed to be able to sign the informed consent form. Although in previous trials, the researchers had found that nearly all the participants could read, in this trial, they found that the literacy requirement was slowing down recruitment considerably. FHI agreed that women who could not read could be enrolled if there were a witness to each woman giving consent. The witness could be someone of the woman's choice or one of two participant advocates from the HIV/AIDS NGO, Association Des Amis Solidaires MERO (Friends Solidarity Association).

**HIV care and treatment.** The PrEP trial screening and enrolment consent forms stated clearly that the participants would receive treatment for curable sexually transmitted infections (STIs) and would not have to pay for visits to the research doctor or clinic staff for health problems related to being in the trial. It also stated clearly that they would not receive treatment for HIV, but would be referred “for help.” If they needed “more help” than the research doctor or clinic staff could provide and were referred to another clinic, they might need to pay. When the social science research found that women were having difficulty accessing services for which they were referred, a health advocate was hired (in October 2004). The health advocate was available to accompany participants to services for health or other concerns.

The trial had a “good faith” agreement with a local hospital for care but no formal agreement defining the scope of treatment or who would cover the cost. The

study investigator was the medical director at a local hospital, and he agreed that his facility would care for participants who became HIV infected during the trial, in keeping with the standard of care available in the community at the time.

**Ongoing social science research.** The social science research continued during the trial. The researchers monitored adherence, interviewed participants to assess their understanding of the trial, interviewed those who discontinued, and explored community rumours and concerns. Interviews related to informed consent found that, as in all trials, participants' levels of understanding varied. For example, despite repeated explanations to the contrary by study staff, they found women who believed that they would be protected by the pill. This therapeutic misconception, or “wishful thinking,” has been documented in many other studies.<sup>21</sup> When they discovered such problems, the social scientists informed the clinical trial team so that they could work to clarify and improve participants' understanding.

## The XV International AIDS Conference in Bangkok, July 2004

While preparing the July issue of Protocol Sud, focused on Cameroon, Act Up-Paris and REDS debated what they could do about the tenofovir trial. Around the same time, Act Up-Paris was contacted by Cabiria, a sex workers' group in France that was in touch with the Women's Network for Unity, a sex workers' group in Cambodia. They had some questions and concerns about a proposed trial among sex workers in Cambodia: the oral tenofovir PrEP trial. Act Up and the Women's Network for Unity got in touch and met soon afterward in Bangkok at the XV International AIDS Conference. There they decided to do a joint protest—to go to a symposium sponsored by Gilead and draw attention to their concerns by taking over the stage. Consistent with Act Up's style, the tactic was provocative and geared toward attracting media attention. The following day, they participated with treatment activists in occupying the Gilead booth; the booth was covered in fake blood and some property was destroyed. Afterward, they wrote a press release with the Asian Pacific Network of Sex Workers, which they distributed at the closing ceremony.

The press release was Act Up's first written statement of concern. They and the Asian Pacific Network of Sex Workers accused Gilead Sciences of conducting trials on “sex workers outside of all ethical rules.” They denounced the very idea of trials among “sex workers”

21. See, for example, Applebaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. *IRB*. 2004;26(2):1–8.

in developing countries, because of their social and legal vulnerability. Because the women might believe that the pill would be protective—despite researchers’ explanations and counselling—they argued that participation placed the women at even higher risk of infection. The press release went on to make a series of assertions. First, treatment for sexually transmitted infections and compensation of US\$3 for transportation and time constituted undue inducement, and hence, interfered with the women’s ability to freely give consent.<sup>22</sup> Second, the prevention package offered to the participants was inadequate—because it did not include female condoms, individual counselling, or strategies for female empowerment. Third, the activists deemed that having only five social workers to counsel 100 participants was inadequate.<sup>23</sup> Finally, the health care provided was “unethical” because it did not include antiretroviral therapy for participants who seroconverted during the trial or for those who were screened out because they were already HIV positive.

They demanded that as long as the trials were being conducted in this way, all of the tenofovir PrEP trials be stopped immediately.<sup>24</sup>

### **Attempts to resolve issues and missed opportunities following Bangkok, mid to late 2004**

At the Bangkok conference and in the months that followed, many suggestions were made for dialogue among the researchers, advocates, activists (not all of whom agreed with what Act Up-Paris was doing), representatives from the Gates Foundation, the US National Institutes of Health, and Gilead Sciences. Some attempts were made, but no discussions took place that could have resolved the issues. The activists felt a sense of urgency because the Cameroon trial site was continuing to enrol participants without its concerns having been addressed. Act Up-Paris informally agreed to hold off on further action until December 2004 in order to allow time for dialogue, but none of the major parties were able to convene a discussion before this deadline.

A strategic decision was made for the Joint United Nations Programme on HIV/AIDS (UNAIDS), as a

neutral broker, to convene a meeting of all parties. Major stakeholders had differing views about what should be addressed and accomplished at such a meeting. Ultimately, the UNAIDS meeting evolved into a broader discussion of “partnerships” in clinical trials. It was preceded by a series of regional meetings during the spring of 2005. Although the international meeting was initially planned for December 2004 and then February 2005, it did not take place until June 2005. In the meantime, the International AIDS Society (IAS) planned a meeting to tackle some of the specific issues in the tenofovir PrEP trials, supported and hosted by the Gates Foundation in May 2005. It included investigators from the trial sites, sponsors, donors, Ministry of Health representatives from each of the trial countries, and activists from trial countries, as well as Act-Up Paris and other international advocates that had become engaged.

Notes from a conference call among activists, funders, and researchers in October 2004 observed:

Unless substantial dialogue is started now between researchers and community groups on the ground on the specific issues raised over the past few months, when we get together in February (for a planned consultation) we’ll have wasted another two - three months waiting to deal with these thorny issues which threaten to derail not only the tenofovir studies, but could really impede the progress of research on a wide range of prevention interventions.<sup>25</sup>

This prophetic warning went unheeded, and no substantive dialogues aimed at specific problem-solving were started. The meetings ultimately occurred too late to prevent the suspension and closure of the Cameroon trial site. In hindsight, several key actors have noted that this was a period of missed opportunities.

### **Back in Cameroon, December 1, 2004, World AIDS Day**

In the meantime, Jean-Marie Talom and Calice Talom from REDS tried to follow up with the researchers in Cameroon. What, they asked, was happening with the trial; and what, if anything, was being done to address the activists’ concerns?

Months passed in which they could not get meetings or satisfactory additional information. They then

22. In contrast, the Cameroonian activists and the Cambodian sex worker activists thought that the level of compensation was far too low.

23. This was the figure cited in the Act Up-Paris press release from Bangkok; in fact, the site in Cameroon employed five counsellors for 400 participants. The researchers felt this was sufficient, as on average, each counsellor saw about five women per day (see discussion on page 29).

24. Gilead organise la contamination des travailleuses du sexe [press release]. Paris, France: Act Up-Paris; July 16, 2004.

25. In an email from Gregg Gonsalves (October 25, 2004): Thoughts on our tenofovir call today.

turned to organisations working on women and AIDS, and discussed the tenofovir trial several times with a network of AIDS NGOs. These groups did not seem to understand what the issue was, or what was at stake. REDS approached a number of journalists, but few seemed interested in following up.

Jean-Marie Talom and Calice Talom also started looking for alternative ways to obtain information about what was happening in the trial. Some of their information came from people directly connected to the trial—sources that they later said could not have been cited officially because doing so could have jeopardised their positions. They also requested a people living with HIV/AIDS group to obtain information for them—which they did.

Initially, the two REDS activists were reluctant to make use of this largely anecdotal and non-verifiable information. The activists say that after several efforts to follow up with the researchers to determine if anything was being done to address their concerns, they were informed that only the principal investigator could discuss the trial—and that he was travelling and did not have time to speak with them. The local researchers maintain that they met with and discussed the trial with the activists from REDS and Act Up-Paris several times. As matters evolved—and in the continuing absence of information from attributable sources—the activists did use the anecdotal information in their critique of the trial.

On World AIDS Day 2004, REDS published an article in a Cameroonian newspaper that restated previous concerns about the trial. The research team in Cameroon met with staff at REDS to discuss the article. FHI reports that the local research team drafted a lengthy response to the article in *La Nouvelle Expression*, a national newspaper, but decided not to submit it for publication to avoid further fanning the flames.

## France 2's television coverage, end of 2004

Toward the end of 2004, a programme on the television channel, France 2, was planning a story on “big pharma,” and the producers contacted Act Up-Paris for potential ideas.<sup>26</sup> Knowing the programme's reputation for sensationalism, Fabrice Pilorgé acknowledged his discomfort. On the other hand, no progress had been made toward addressing Act Up's concerns, and the

activists felt that something needed to be done urgently. A “media circus” was seen as a legitimate means to draw attention to issues that were otherwise being ignored. So Act Up-Paris told France 2 about the oral tenofovir PrEP trial and pointed them to the main players, including FHI and REDS.

The France 2 journalists approached FHI and said that they wished to produce a programme on the Cameroon portion of the West African trial and the development of new HIV prevention technologies. FHI took this explanation at face value, although they also were aware of the programme's sensationalist style. FHI provided information, including access to the trial sites and researchers. The only condition, which is a matter of institutional policy on participant privacy, was that trial participants would not be made available for interviews.<sup>27</sup>

While the journalist was in Cameroon, a study participant contacted the researchers to complain that she was being asked questions by a reporter despite the trial's guarantee of confidentiality. Why, she asked, was a journalist contacting her? Suspecting that she had been followed from the research site in violation of the agreed conditions,<sup>28</sup> the researchers realised that the journalists were not being transparent about their motives. Consistent with FHI's approach of responding to media requests and working transparently, they did not try to stop the journalist's access to the trial. The REDS activists, Jean-Marie Talom and Calice Talom, accompanied the journalist on some of his interviews.

The France 2 programme aired in France in January 2005. It portrayed an exploitive trial driven by pharmaceutical greed and profit-seeking. Act Up-Paris saw the programme as too sensational and exaggerated in areas. A Cameroonian researcher described the programme as “very violent and implied a lot of things which were very distorted.” The Cameroonian government criticised the television report and the activists, and it defended the trial.

## Protest at the embassy and aftermath on the Internet, January 2005

Act Up-Paris contacted REDS after the France 2 programme aired to find out what was happening and

26. Despite repeated efforts to reach the journalist who produced the France 2 programme, our calls were never returned and we were unable to interview him. The information presented here comes from interviews with activists and researchers.

27. Interviewees indicated that US Food and Drug Administration (FDA) policy would not allow trial participants to speak with journalists. FDA policy does not, in fact, prohibit this, but researchers are concerned that interaction between participants and the media could influence the results, and thereby undermine trial validity, and so tend to be extremely cautious. Many trials also ensure participant confidentiality as part of the enrolment process and take this commitment very seriously.

28. According to FHI, France 2 had agreed in writing not to try to interview trial participants, and the head of the national ethics committee sent a letter stating that it was unethical to interview participants, yet they did anyway.

to offer further support. With little immediate reaction in Cameroon and the government stepping in to defend the trial, Act Up-Paris decided that something more was needed to draw attention to its concerns. They hastily organised a protest at the Cameroonian embassy in Paris. Only five people showed up, with no press. The protesters nevertheless entered the embassy. After a short, violent struggle, they were ejected amid derogatory slurs. Act Up-Paris members themselves called the police and some press agencies, and they issued a press release. In turn, the Cameroonian embassy protested officially to the French government, and the Cameroonian ambassador to France reportedly called Cameroon to find out what was going on.

While Act Up-Paris considered their protest a “disaster” at the time, the ensuing press coverage deeply concerned the North American activists and FHI. When news of the protests and the press coverage hit the Internet listservs, it became clear that the Cameroon site was in serious and imminent jeopardy. The Cambodia trial preparations had already been halted. Negative coverage of a PrEP trial in Thailand among injecting drug users had been circulating over listservs since November. Prevention advocates such as the Global Campaign for Microbicides (GCM) and the AIDS Vaccine Advocacy Coalition (AVAC) became increasingly concerned, fearing a cascading effect on prevention research.

Indeed, as described below, this is exactly what happened. The protest and the accompanying press coverage hit a nerve in Cameroon, tapping into a deep vein of suspicion and distrust around international research.

## Media coverage, early 2005

Suddenly, the issue caught fire in Cameroon. Talk of the trial was all over the Cameroonian media and it became a hot topic of public discussion. The factual basis of the reporting was uneven. Some journalists contacted the activists and the researchers who were actually involved. Most did not. Some quoted other groups or activists that had not been involved up to that point, and some apparently made up whatever they wished. With the rumour mills working overtime, misinformation and allegations abounded—for example, that trial participants were being injected with HIV and that researchers were hiring HIV-infected men to be their sex partners. Evidence, proper sources, and fact-checking were largely set aside.

The misinformation about the oral tenofovir trial erupted in a historical climate of mistrust in science and clinical research in Cameroon. Several interviewees noted that there had been scandals and accusations surrounding injections and vaccination programmes over the years, fomenting distrust in health systems and technologies. This was coupled with a general belief that reports made by the media are “true”—so that many people believe that if a reporter has written something, he or she has witnessed it personally.

Many people raised questions about the trial and criticised the government for approving the trial in the first place. They called on the government to act. This created significant political pressure, especially on the minister of public health, to demonstrate decisiveness and act in the face of the increasingly loud and inflammatory public debate. In late January 2005, several days after the embassy protest, the Cameroon Ministry of Public Health announced the temporary suspension of the trial. An audit commission was appointed to investigate and report back in ten days.

## Government audit commission and suspension of the trial, February 2005

In early February, the audit commission reported back to the Ministry of Public Health. The minister then issued an official decision to suspend the trial due to “deficiencies and dysfunctions observed by the Audit Commission.” The following corrective actions were made conditions for lifting the suspension:

1. The trial centre should be declared as a medical office.<sup>29</sup>
2. The participant information sheets should be made more explicit and comprehensible.
3. Female condoms should be part of the prevention package.
4. The administrative, medical, and psychosocial hierarchies and responsibilities of the research team members should be clearly defined.
5. The coordinator should supervise more rigorously, including holding monthly coordination meetings with reports forwarded to FHI and various governmental bodies.
6. Quarterly progress and side effects reports should be sent to the same.
7. HIV/AIDS prevention associations in Douala should be invited to collaborate on the counselling and

29. The trial site had been set up separate from a formal medical facility to respond to participant concerns about privacy, stigma, and convenience. However, government policy is that all health care facilities must be registered with the government, and it had not been formally registered as such.

participant support activities, particularly with screen-outs and seroconverters.

8. Relations with accredited treatment centres should be formalised.
9. FHI and Gilead should “decide on the availability and accessibility of [tenofovir] for African countries.”

The audit commission did not identify any ethical problems per se with the trial. The actual report of the commission’s findings was never made public.

## Reaction to the suspension, early 2005

Between the XV International AIDS Conference in Bangkok in July 2004 and the end of January 2005, there had been a relatively muted level of interest and back-and-forth among international advocates and activists and on listservs. The suspension of the trial, however, caught their attention and this activity picked up substantially. In mid-February, the Global Campaign for Microbicides (GCM) and the AIDS Vaccine Advocacy Coalition (AVAC) issued a statement that argued that shutting down trials was not the solution. They proposed instead that new research standards be developed and funding demanded to enable trials to meet those standards. They also noted that some of the statements in the press had been inflammatory and not based on or backed by evidence. In March of 2005, GCM’s executive director went to Paris to meet with activists from Act Up-Paris and AIDES<sup>30</sup> in order to share information, and to understand and find out more about their concerns and critique, particularly the evidence for those concerns.

## The second inquiry, February 2005

Following the report by the ministry’s audit commission, the Cameroon National Medical Council (CNMC or le Conseil de L’Ordre des Médecins du Cameroun) decided to undertake its own independent inquiry. CNMC set up a commission to examine whether the research methods met national and international standards. Their stated goals were to collect the maximum information on the research, find out if there were any violations of ethical norms, and identify the sources of the controversy. They interviewed the major players in the research and in the

controversy. Additionally, and with the cooperation of the researchers, they interviewed about 40 participants in the study under strict confidentiality.

The CNMC gave its report to the Ministry of Public Health, and CNMC’s president, Dr. Daniel Muna, held a press conference on the findings. He reported that the committee had identified some ethical deficiencies but declined to discuss the details until the minister had reviewed the report. Dr. Muna clarified that contrary to rumours circulating among the public, participants in the trial were not injected with anything and that the study pills did not contain HIV. Dr. Muna said the committee recommended that the clinical trials be resumed if the sponsors rectified “certain things” that the commission had identified.<sup>31</sup> The report was never made public, nor were the researchers ever informed of the specific issues or “violations” that needed to be rectified.

The Ministry of Public Health agreed that while no active or placebo drug would be distributed, the researchers could continue to provide condoms, counselling, and health care for the participants while waiting to find out if the trial would restart. After the suspension of the trial, many participants returned each month despite the fact that they were receiving neither product nor placebo. According to the researchers, 75–80 percent of the participants came for their last visit in August of 2005, six months after the study had been suspended and they had been taken off the drug.

At the time the trial in Cameroon was suspended, ten participants had seroconverted, six of whom were in the placebo arm of the trial and four of whom were in the tenofovir arm.<sup>32</sup> The researchers report that most of the women said they believed they became HIV positive with their regular partners, with whom they reported not using condoms. FHI now has a formalised contract for these women to access treatment and care paid for by FHI. The contract, with a hospital in Douala, states that the “women will be provided with access to HIV/AIDS state-of-the-art care and treatment, as defined by the Cameroon National AIDS Programme.” The hospital is contracted to offer the women access to ten years of priority pre-treatment HIV care, including medical consultations, counselling sessions for nutrition and psychosocial care, home visits, initial and follow-up laboratory work, and treatment for opportunistic infections. It

30. AIDES is a Paris-based NGO that works on advocacy and service provision for prevention and treatment throughout France and in a number of countries in Africa. AIDES had gotten involved with the tenofovir trials through its ongoing relationships with Act Up-Paris and colleagues in Cameroon.

31. Douala AIDS drug controversy: Medical Council says trials violated ethical norms. *The Post* (Buea, Cameroon). February 24, 2005.

32. Combining the results from the trial sites in Cameroon, Ghana, and Nigeria, there were 14 seroconversions. Eight of these were in the tenofovir arm and six were in the placebo arm. Of the eight in the tenofovir arm, four were in Cameroon, three were in Ghana, and one was in Nigeria. Of the six in the placebo arm, all six were in Cameroon. These results are not statistically significant.

is also contracted to provide five years of HIV ARV drugs over a period of 15 years, ending at the end of September 2020.

### **FHI follow-up, February–December 2005**

After the trial was suspended, FHI's president, Ward Cates, went to Cameroon in February 2005 to work with the researchers to address the issues identified by the ministry's audit commission. The researchers took the ministry's list of nine issues at face value and worked to make all the requested changes. They submitted these modifications to the Ministry of Health.

A meeting was held on February 14, 2005, with all key parties—the minister of public health, the local formative and clinical research leaders, the president of FHI, the head of the audit commission, and other directors of health departments. Despite having a verbal agreement from the audit commission head that all nine issues had been successfully met or answered, at the meeting, he was unsupportive of resuming the full trial. The minister agreed to allow study participants to be followed, but no study drug could be distributed.

After waiting six months for an official response from the ministry that distribution of the study product could be resumed, participants had been off the product for so long that the data were no longer useful scientifically, and so FHI closed the trial officially in August of 2005. The ministry has never responded, giving the impression that additional unarticulated political factors were at play, something some ministry officials confirm off the record.

FHI also provided financial support for a meeting of Cameroon stakeholders to define HIV prevention research priorities in Cameroon, held in December 2005. The need for such a meeting had been identified by Cameroonian participants at the IAS consultation hosted by the Gates Foundation. Participants, including Ministry of Public Health officials, researchers, journalists, NGO representatives, and health care providers, discussed standards for HIV prevention and medical care for research participants, research literacy, research ethics, community involvement, and communication. In terms of standard of care, the meeting participants recommended that volunteers screened out of a trial because they are HIV positive should receive a health check-up and be enrolled in the national HIV treatment and care programme (on terms negotiated prior to the start of recruitment); trial participants should receive free care for all study-related serious side effects; and participants who seroconvert during the trial, their partners, and dependents should be provided with complete HIV and AIDS care for life by the research implementers and the government. In relation to community involvement, the meeting recommended developing community participation guidelines; creating a legal framework to protect the rights of minorities and vulnerable people; and creating community advisory boards with defined scopes of responsibilities, terms, and conditions. The two top priorities for national HIV prevention research identified at the meeting were social and behavioural research, and biomedical research on microbicides and female condoms.



### 3. Competing narratives

The story of the tenofovir trial in Cameroon reflects the complexity of the factors and the diverse actors that played a role in its development and eventual demise. This section lays out the perspectives of

many of the individuals and institutions involved. It is organised by roles, each of which includes a range of individuals, and in some cases, groups, with diverse and sometimes divergent views and interpretations regarding the events. We have tried to reflect the richness of these perspectives in the sections that follow.

#### Family Health International

Staff from FHI brought a range of perspectives and expertise, from social and clinical science to epidemiology and policy. We interviewed many but not all of the FHI staff who were involved in the trial.

FHI intended the tenofovir trial to be a “state-of-the-art” prevention trial and invested a great deal of time and resources in social science research in addition to the clinical trial. As the trial and controversies evolved, an ever-increasing range of organisations and actors inside and outside Cameroon criticised the trial. This atmosphere of intense critique and sometimes inflammatory accusations raised complex questions for FHI of whom they needed to involve, what they needed to respond to, and which issues they needed to address.

#### Formative research and community consultation

Recognising the clinical and social complexity of HIV prevention trials, FHI included significant formative research to systematically gather community input to inform the trial design, and importantly, to inform how the trial findings might be translated into effective and acceptable prevention interventions. FHI believed that this effort went well beyond the norm for clinical trials, so they were particularly surprised when they were criticised for not doing enough community consultation.

In the escalating debate about the trial, FHI mentioned the extensive research they had done to understand the local community and be responsive to the concerns of the women enrolled in the trial and found it frustrating that this was not acknowledged. In addition, the Cameroonian colleagues who had designed and implemented the social science work with FHI were not included in the consultations convened by the International AIDS Society or UNAIDS, so their perspectives and contribution, especially the insights

they could provide on how the controversies were unfolding in the local communities, were not fully recognised or appreciated.

Using the findings of the formative research, FHI worked to be as responsive as possible to potential participants’ expressed needs. It seemed ironic to them when they were later criticised for things that they had done to meet the study population’s expressed preferences. For example, locating the study clinic outside a hospital setting by establishing a separate, discreet clinic was a direct effort to respond to concerns about maintaining privacy and convenience while avoiding stigma. However, this was later perceived and described as an effort to keep the trial “secret” (the study clinic was identified only by a small sign).

At the same time, FHI was under considerable pressure from the scientific and public health community to get the trials going quickly. A shared sense of urgency existed to find an intervention that would prevent HIV infection in women—as it does today. Some FHI researchers acknowledged that the relative speed with which the research was designed and developed affected the extent of community preparation and the degree to which formative research results could be incorporated into trial processes.

FHI’s approach to community consultation consisted of conducting qualitative research in the trial site community. It defined the “community” as the women who were potential participants in the trial and the key actors who surrounded them—their partners and families, policymakers, and health and AIDS care providers in the areas of Douala where the women lived and worked. FHI and its partners intentionally designed this research process to allow them to hear the perspectives of the potential and actual trial participants directly. Women at high risk for HIV were not organised in this setting, and other organisations that may have represented the women’s interests did not emerge during the preparatory work. The researchers believed that the women should speak for themselves and that they could serve as their own advocates, although one researcher later acknowledged that this may have been unrealistic.

FHI did not engage in a broader stakeholder or civil society consultative process, and did not set up a community advisory board or other structures for

ongoing community involvement in the implementation of the trial. In retrospect, some staff at FHI thought that a broader stakeholder mechanism would have been helpful, while others questioned whether such a political process would have really served to represent the interests of the marginalised and vulnerable women in the trial. The criticisms also raised the question for them of how broadly researchers need to consult and involve the “community.”

The deliberate separation of the social science research from the clinical research meant that few people in the community—even those who were interviewed during the formative research—associated this process with the actual trial. Views at FHI on whether this separation was appropriate remain mixed: some feel the two processes should have been more integrated, while others continue to see the separation as essential to maintaining the objectivity and integrity of both the social science and clinical research. Regardless, it was clear that the formative research was not perceived by the community as a process of “engagement” around the trial. The experience with the Cameroon site underscored that social science research is not a substitute for a well-considered plan to meaningfully involve communities and other stakeholders in the research process.

### Clinical trial protocol and implementation

**Informed consent.** From FHI’s perspective, the trial processes and trial staff worked hard to ensure that trial participants understood the trial. Researchers and trial staff informed the participants about the trial purpose, risks, and procedures; assessed their understanding on an ongoing basis; and worked to correct any identified problems. For example, the social science team identified therapeutic misconception—where participants thought the drug might protect them from HIV infection—as an area of concern, and the trial worked to strengthen this component of the informed consent and counselling.

The informed consent booklets were first translated into French prior to the beginning of the formative research, during which they were tested, refined, and re-translated several times. In the weeks prior to the trial, when Act Up-Paris and REDS were given English versions of the booklets but not French ones, the finalised booklets were being re-translated and back-translated. FHI is required to submit informed consent documents in all trial languages, along with a document vouching for the accuracy of the translation, to its IRB before they can be used in the field.

Researchers at FHI remain perplexed about why Act Up-Paris and REDS continue to maintain that the informed consent document was only in English. According to FHI, neither Act Up nor REDS ever contacted them to request the French translation, but FHI responded promptly to at least two other requests. FHI indicates that Act Up-Paris was copied on emails in October 2004 stating that FHI had sent SIDACTION, an NGO in Paris that works closely with Act Up, English and French translations of the informed consent documents and the protocols for the clinical trial and formative research. A reporter from the French newspaper *Le Monde* who had heard the concern about the informed consent documents from Act Up-Paris contacted FHI in February 2005, and FHI sent the French and English forms the same day. FHI finds it puzzling that Act Up-Paris did not access the translated informed consent, which also was available on two French AIDS websites, or make an effort to contact FHI directly.

**Prevention package.** Study staff thoroughly counselled participants on HIV prevention and provided them with an unlimited supply of male condoms, the best known prevention method for sexually active people. While most of the materials were initially developed in English and translated (because it was a multi-site trial with several languages), FHI states that counselling for participants or potential participants, including informed consent, was always provided in the participant’s chosen language, usually French. As described, female condoms were not included in the prevention package. The female condom was not widely available in Cameroon, nor was it included in the standard of prevention that FHI and other researchers used in many other prevention trials.

After the audit commission, the government recommended that the risk reduction counselling be contracted out to a separate entity in an effort to reduce any potential for bias in the counselling.<sup>33</sup> FHI researchers felt strongly that providing risk reduction counselling and services was a crucial ethical obligation—their obligation—to the trial participants. As such, they felt that in order to ensure that the women in the trial were receiving the best possible counselling and services, the trial needed to provide it directly. They felt they could not delegate this crucial ethical responsibility. When FHI responded to the government’s recommendation and approached other groups that could potentially be contracted to conduct the risk reduction counselling, it was perceived as trying to “buy” these groups’ cooperation.

**Access to treatment for seroconverters.** While the activist groups charged that not guaranteeing provision of antiretroviral

33. Because HIV prevention trials require a certain number of participants to seroconvert and become HIV infected during a trial, some activists have questioned whether researchers and trial staff may have a conflict of interest in providing HIV risk reduction services. One proposed approach to address this concern has been to contract this component of the trial to another entity to reduce this so-called “researchers’ dilemma.”

therapy for women who were HIV positive at screening or who seroconverted during the trial was unethical, FHI understood its ethical obligations as needing to provide referral to the best local care and support services. FHI notes that its institutional review board in fact insisted that the informed consent form explicitly say that the trial would not provide antiretroviral therapy to participants who became HIV infected, to make this clear to potential trial volunteers. They considered that providing antiretroviral therapy in a context where it was not generally available would represent undue inducement and therefore be unethical.<sup>34</sup>

FHI underscored that expectations and norms about access to treatment—in general and in the context of prevention trials—were evolving rapidly throughout the time that the tenofovir trial was being developed and implemented. Given this, some felt they were being held to a standard that was neither widely agreed on nor anticipated when the trial was designed and the protocol written. FHI reported that in retrospect, it would have made its agreements for treatment and care much more formal and concrete and done so more rapidly than it did. In addition, it was not clear to FHI, or to others, what the precise standard or mechanism would be for meeting trial participants' needs for treatment, sometimes many years after the end of the trial (see Box 3, “The changing treatment environment”).

### Relations with activists and media

**Transparency and confidentiality.** FHI found it especially frustrating that they never saw hard evidence to substantiate many of the allegations that were raised by activists or circulated widely in the press and on the Internet. It was not clear to them where or how the activists got their information, and whether alleged concerns were based on actual experience, and if so, the experience of one person or many was never substantiated. They felt that a double standard existed: FHI was asked and expected to be transparent and responsive, but when the activists were asked to be equally clear about the sources and extent of their evidence, these were not provided.

From FHI's perspective, maintaining participants' confidentiality was central to trial ethics and meeting Good Clinical Practice regulations. They interpreted this obligation to mean that trial participants could not be identified to or interviewed by outside organisations.

While this may have created an impression among some activists or media that there was “something to hide,” FHI would not compromise.

As noted previously, FHI felt that it had been intentionally misled by the producers at France 2 about the story they intended to tell and that the trial was seriously misrepresented in the France 2 programme, as well as in much of the other media reporting. FHI sees the France 2 broadcast as the beginning of the media firestorm that rapidly spiralled out of control, completely tainting the trial. At the same time, they realise that some of the researchers who were interviewed said things that did not reflect well on the trial, and that despite some media training, neither the researchers nor the institution were adequately prepared to deal with the media.

### Overall responsiveness to concerns

In considering their responses to the concerns raised by the trial, FHI staff acknowledged that some real mistakes were made. First, FHI recognised in retrospect that they had not taken the concerns raised by the activists seriously enough, quickly enough. This was in part due to the confrontational style and rhetoric used by the activists in Bangkok.

FHI also noted that in responding to immediate concerns about the trial stoppage, it had focused on the government and its recommendations, and not on the other actors in Cameroon or internationally who had raised the concerns that had prompted the government investigation. They acknowledged that they did not look beyond the government's specific recommendations to the broader political context. Finally, FHI commented that, in retrospect, they wonder whether the trial could ever have resumed delivering study product. Although the list was framed as recommendations for restarting the trial, it seemed that by that time, things had already spun so far out of control in the public arena that realistically, the government would likely never have been able politically to allow the trial to resume.

### Why *this* trial?

FHI acknowledged that the West African trial was not perfect, but saw that like all trials, it had rigorous and well-functioning systems in place to monitor trial processes and to identify and correct problems as they emerged. In fact, given the extensive social science component that allowed for assessing and monitoring a

34. The issue of whether and how the provision of antiretroviral treatment in settings where it is not otherwise available might affect the voluntariness of decisions to participate in HIV prevention trials was a subject of active debate at the time. More recently, ethicists have come to question the notion that providing health care that is not available locally necessarily undermines voluntariness. Rather, it depends on the risks that participants are asked to assume, balanced against the benefits that participants would receive. Inducements only become problematic if they encourage individuals to assume risks that they otherwise would not. At the same time, the specific issue around access to antiretroviral therapy as an “undue inducement” became less of a concern as access to antiretroviral therapy became more widespread.

## The changing treatment environment

FHI's tenofovir PrEP protocol was approved in early 2002 against a backdrop of rapidly evolving expectations and possibilities for access to antiretroviral therapy for people with AIDS. Concerted activism and growing recognition of the devastating impact of the AIDS epidemic was radically shifting the norms for antiretroviral therapy in resource-limited settings. Once dismissed by many international health leaders and policymakers as neither affordable nor feasible, access to antiretroviral therapy became a priority, championed by a number of world leaders.

In the time between the Gates-sponsored ethical consultation on the tenofovir trials (November 2001) and enrolment in the Cameroon trial (July 2004), several critical international efforts to advance access to antiretroviral therapy were launched: the Global Fund to Fight AIDS, Tuberculosis and Malaria (2002); the US President's Emergency Plan for AIDS Relief (2003); and the World Health Organization 3 by 5 Initiative (2003). However, even as these programmes got off the ground, a great deal of

uncertainty continued about the specifics of global financial commitments, drug prices, service delivery capacity and mechanisms, and other key issues related to implementing widespread provision of antiretroviral therapy.

During these uncertain times, trialists, ethicists, and activists continued to debate, and disagree on, whether providing antiretroviral therapy to participants in prevention trials who seroconverted was an ethical imperative. Although a few HIV prevention trials worked to ensure treatment for participants, at the time, few, if any, vaccine or microbicide trials being developed and implemented did so. In fact, given that treatment was not widely available, some of the ethics discourse at the time maintained that offering treatment in the trial that was not available through the public health system would be undue inducement for people to enrol in the trial. There is now greater consensus on provision of treatment being feasible, ethical, and politically indicated, but this debate was very active and unresolved at the time the protocols for the tenofovir PrEP trials were being developed and the West African trial was being implemented.

wide range of issues, they saw this trial as having more capacity to do so than most.

FHI expressed real curiosity and reflection about why this trial in particular prompted such scrutiny and became such a lightning rod. Some hypothesised that as an antiretroviral drug, tenofovir attracted the attention of treatment activists working to expand access to treatment, including tenofovir, more broadly. The activists were concerned about the limited access to tenofovir for treatment and Gilead's unwillingness to drastically reduce the price, and were experienced in getting media attention.

The controversies around the tenofovir trials exacted a high institutional and personal toll on many of the people involved in the trial. FHI underscored that the tenofovir PrEP research was driven by public health concerns, and the individuals and institutions involved were working with public-sector and philanthropic funds, not for profit. They expressed real dismay that the Cameroonian staff and the study participants had been portrayed so negatively by local authorities and in the press. Overall, FHI staff seem to view the events around the West African tenofovir trial as a difficult chapter, but they also provided a real learning experience for future HIV prevention trials. The trial was a missed opportunity to answer a critical research question about the effectiveness of a new prevention option that might have the potential to save many

lives. However, it did make an important contribution to PrEP research through collecting enough data on safety to provide a springboard for future HIV prevention trials.

### Cameroonian researchers

Cameroonian researchers involved in the West African oral tenofovir PrEP trial generally had quite consistent perspectives on what happened and why, though they varied on some points. This section reflects some common themes they touched on.

#### The trial

Overall, the Cameroonian researchers involved in the tenofovir PrEP trial felt that in terms of the science, nothing was wrong with the trial or their work. They were experienced researchers who had done clinical trials before without problems. In addition, they had the required authorisations and approvals from the ethics review boards and government authorities.

The researchers noted that through counselling and interviewing participants during the study, they were aware that there were some minor problems in the trial implementation. For example, they knew that a few study participants were not taking the pills, or did not have the required number of sexual partners. In monitoring

the study, the social science research team found varying levels of understanding about the unknown effectiveness of the pill for prevention. From their perspective, the goal was to identify problems and use the information gathered to improve the counselling and research as a whole. They did not see these issues among a few women as problematic enough to necessitate contracting out the counselling or stopping the trial.

Most of the Cameroonian researchers, but not all, felt that the formative and clinical research teams should not have been separate. In particular, they felt that (1) the clinical trial team needed to be more aware of what the formative research team was doing and finding; (2) more formative research was needed; and (3) more time was needed between the two phases for analysis and for the findings to be more fully integrated into the trial.

### Relationships with others

**International researchers.** Because this was a multi-site trial developed by FHI, the Cameroonian researchers noted that researchers at any one site did not always have a complete picture of the trial. This became problematic when they were asked questions and held responsible for details on how the trial was planned and implemented. When the trial became an issue of public debate, no one from FHI was on the ground in Cameroon to support the researchers or respond to questions and concerns directly. For their part, the Cameroonian researchers were not always certain about the extent of their authority and responsibility for representing the study.

They noted that when funding comes from outside the country (and even more so in multi-site trials), external exigencies can outweigh the local situation and knowledge. For example, when the FHI principal investigator said that changes, such as those proposed by the activists, could not be made, they accepted the decision since the principal investigator had the authority. In hindsight, they felt that local researchers must have a greater say in how a trial is developed, implemented, and adapted because they know the situation, especially politically.

**Activists.** Because activists had not previously played a role in research in Cameroon, the Cameroonian researchers said that they did not take the activists as seriously as they should have. Some researchers acknowledged that they had a somewhat “What do they know?” attitude toward the activists. They did, however, raise the activists’ concerns with FHI as noted above. Their own perspectives on the specific issues raised were:

- **Concerns about Counselling.** The Cameroonian researchers did not agree that the number of counsellors was too low. There was one counsellor per 80 participants; and therefore, each needed to counsel about five participants per day. While the initial visits required more time, follow-up visits usually took 45–60 minutes, which they thought was appropriate to meet the needs of the study participants and feasible in a work day. They also thought that the counsellors did not have a vested interest in the outcome of the trial that would influence the quality of their counselling.
- **Provision of female condoms.** Overall, the researchers agreed in principle with providing access to more options for prevention. However, according to the researchers, female condoms were not generally available in Cameroon, so they were concerned about trial participants getting used to them when they would not be available after the study.<sup>35</sup> Some also were of the opinion that study participants may not be interested in using the female condom because they were not familiar with it.
- **Treatment for seroconverters.** The local researchers noted that the care and treatment provided in the trial did follow standard ethical guidelines: that researchers are not obliged to provide treatment for conditions not caused by the study product, but are expected to refer patients for the best available treatment. If the ethics review committees had asked them to do otherwise, they would have done so. They agreed that seroconverters should be provided antiretroviral therapy, while noting that this was a new standard for which national and international guidelines were needed. They also remarked that requiring the provision of antiretroviral therapy could create logistic and resource challenges for local researchers, possibly preventing Africans from conducting their own studies.

In the end, they believed that Act Up-Paris and REDS started with mistrust toward them and that the activists’ main goal was to shut down the trial. Some were put off by the Cameroonian activists’ communication style and by the lack of accuracy in some of their claims; one noted that just because the activists said something, that did not make it true. Finally, one person raised the question as to what constituency, if any, the two REDS activists actually represented.

**The media.** In the past, the researchers in Cameroon had not done pre-study publicity, education, or outreach to the media, believing as one said that “scientists shouldn’t

35. FHI reports that when they tried to procure female condoms after the suspension of the trial, they found that none were available for purchase within Cameroon. Then, they had considerable difficulty with the administrative procedures necessary to get female condoms into Cameroon, and by the time they did, the trial had shut down.

be noisy guys” and “you talk to the media when you have results.” They had done two previous trials without problems. However, in this case, they noted that because the community was not generally aware of what they were doing and did not understand it, when difficulties arose, rumours started to spread. The Cameroonian media also were not well-informed and have a general tendency to report stories without necessarily going to the proper sources for information or verifying facts.

The researchers were shocked when they saw the France 2 report; they found it “very violent” and full of insinuations and distortions. They thought the journalist edited the interviews in a manipulative way, including only the information that suited his purpose. They remarked that they were not prepared to be communicators, and that, because the trial was not defended publicly, much factual information about the study never got out. The period when the trial was all over the media was quite traumatic and some even feared for their lives.

### Government role

The trial had fulfilled the existing governmental requirements for conducting research in Cameroon, but the researchers thought that insufficient regulations and procedures existed to guide and monitor research—a reality that left them open to criticism. They thought the government was afraid to restart the trial, and therefore, was not straightforward in how it handled the trial after its suspension. If it had actually been a scientific problem, in their opinion, the government would have responded officially. They believed that it had become so politicised, there was really no way to reach a “scientific” resolution.

### Act Up-Paris

International AIDS activists had varied and sometimes divergent points of view about the tenofovir trials. Act Up-Paris was joined by several Act Up chapters from the United States and other French activists at the Bangkok AIDS conference to protest the trials with the Cambodian sex workers. Some American advocates had strong negative reactions to the protests, perceiving them as “white guys from New York and Paris undermining research on an important potential new prevention technology.” However, after extensive discussions, some later became sympathetic to the primary criticisms of Act Up-Paris. Act Up-Paris itself saw its role as supporting REDS and the Cambodian sex workers to get their concerns about the trial addressed. This section presents the perspectives of a range of international activists, with a heavy emphasis

on members of Act Up-Paris, who were the most vocal and deeply involved.

### Activism

**Worldview.** The history and culture of Act Up-Paris played an important role in their perspective. Although many international activist groups see harm reduction as a useful prevention approach, Act Up-Paris has historically been very absolute about messaging around condom use, and stood strongly against the concept of introducing partially effective products. This meant that they approached all new prevention tools that may be less efficacious than condoms in preventing sexual transmission of HIV from a sceptical perspective.

Although Act Up-Paris had worked extensively on clinical trials testing new treatments, they were not well-versed in the specifics of prevention research. The French researchers who advised them also had not been involved in prevention trials. They questioned whether the trials were Phase 2 or Phase 3 trials and did not see why they would be combined. In addition, because ANRS was now requiring them to do so, French researchers were providing treatment to trial participants both during and after the trials they were conducting. Therefore, French activists expected that providing treatment for seroconverters should and could be done (see Box 4, “Access to treatment: different experiences, different expectations”).

**Goals.** Although Act Up-Paris’ *Protocol Sud* and their press release at the Bangkok AIDS conference called for “the immediate end of the tenofovir prophylaxis trials... as they are presently being conducted,” Act Up-Paris says they did not believe they had the power to stop the trials. They indicated that their goals were to bring attention to the specific issues they were raising, to protect the women in the trials, and to improve the trials. They said they wanted to hold “the promoters” accountable, not necessarily the researchers, and to interrupt the trials until their demands were met.

**Strategies and tactics.** The activists made an initial strategic decision to focus their efforts on Gilead. They were not familiar with the other actors, and indeed, had never heard of a large drug trial sponsored by an NGO. Moreover, they knew that fighting “big pharma” would have media appeal. They decided to use ethics as a tool, although they report that their main focus was ensuring the “rights of participants” and “good science.” In retrospect, they noted that calling something “unethical” generated a great deal of attention, but indicated that they might not use that term again.

Although they knew that they would not be able to control the media, they decided to take the risk with

## Access to treatment: different experiences, different expectations

Activists and researchers from France and the United States bring very different expectations about the right to health care to their analysis. In France, good quality health care is considered a right that the government is responsible for providing. The US system, on the other hand, is well-known for its complex and confusing range of private and public insurance providers, which leave many uninsured and without access to health care. This means that the right to quality health care and the government's obligation to provide it are not assumed.

This difference also is reflected in the funding policies of French and US government agencies. The Agence Nationale de Recherches sur le Sida (ANRS, the French government's national AIDS research agency) Charter of Ethics for Research in Developing Countries, issued in May 2002, notes that ANRS will take responsibility for the medical care (follow-up) of participants infected with HIV who are participants in biomedical research that it is funding. Regarding antiretroviral therapy (ART) in particular, it says that the

researcher is to put everything in place so that participants benefit from an antiretroviral therapy access programme for the duration of the study and afterward and requires that the modalities for the provision of health care after the research be specified in the protocol.

By contrast, the US National Institutes of Health does not allow research funds to be spent on antiretroviral therapy. Although some activists asserted that participants in Cambodia and Cameroon were being denied care that the investigators would have had to provide in the United States, in fact, this is not the case. In the US Centers for Disease Control and Prevention (CDC) tenofovir trial in the United States, for example, participants who seroconvert during the trial are referred to local health care providers or public programmes for needed medical and social services. While locally available care is likely to be better in the United States, the trial sponsor, CDC in this case, is not required to provide, pay for, or ensure access to antiretroviral therapy or other care.

France 2 because they felt so strongly that they needed to do something to get their concerns about the trial addressed, and their other approaches—the protests in Bangkok and Paris, meeting with the researchers, and writing their concerns—had not worked. After the France 2 programme was aired, some found it to be overly sensational and recognised that a considerable amount of misinformation was reported in the programme and the media in general.

### The trial

**Rationale and organisation of PrEP research.** Many international activists thought that the sponsors' and researchers' excitement about the potential of tenofovir led to the research moving forward too quickly, without enough thought, planning, and preparation. For its part, Act Up-Paris thought it went forward too much on faith, rather than on a solid scientific rationale, commenting that the FHI protocol read more like a "sales pitch" than a scientific defence of the idea. They did not see tenofovir as "a miracle pill" and believed the funding agencies should have been more rigorous and demanding about a scientific rationale.

**Choice of population.** Act Up-Paris was critical of the trials being conducted on "prostitutes"<sup>36</sup> in developing countries, in particular, where sex workers were not

organised and their rights not recognised. They believed the research would make the trial participants more vulnerable. They noted that there was no justification for the choice of country or trial population in the FHI protocol and observed that it should be possible to do the research in a less vulnerable population. They believed that this population had been chosen primarily because it would be less expensive to conduct the research with them. Some activists also questioned whether tenofovir, if proven effective, would ever be available for prevention in developing countries. They believed that the research would really benefit only gay men in the global North, and therefore, should not be done on sex workers in the global South.

**Community preparation and consultation.** Act Up-Paris did not receive the formative research protocol and it was not mentioned in the clinical trial protocol; therefore, they were unaware that any sort of community consultation had been done. In addition, their view of what effective community consultation involved was quite different from what the researchers did. They stated that a broader spectrum of civil society organisations, including those likely to be critical, such as REDS, should have been consulted, and consultation should have been done before all of the main decisions had been taken.

36. In Cameroon, the women in the trial were to have had an average of three or more coital acts per week and four or more sexual partners per month. Regardless of how the women saw themselves, they were not defined or labelled as "prostitutes" by the researchers but as "high-risk women." The activists, however, consistently referred to the trial population as "prostitutes," reinforcing the stigmatization to which they objected.

**Informed consent.** Many activists believed that the informed consent process was insufficient. When Act Up-Paris was in Cameroon in May, it was given only the English-language informed consent booklets. They maintain that they never received the French translation,<sup>37</sup> and continue to maintain that the counselling and informed consent process was being done only in English for a predominantly French-speaking population. There were some criticisms of the content of the informed consent booklets as well.

**Prevention package.** Act Up-Paris felt that the prevention package offered to participants should have included the female condom. They also thought that there was an implicit conflict of interest in having the researchers provide prevention counselling, because in order for prevention trials to ascertain the effectiveness of the product compared to the placebo, some of the participants would have to seroconvert during the trial. Hence, they believed researchers had a vested interest in participants seroconverting. More women would need to be enrolled in the trials to obtain scientifically valid results if researchers were doing the prevention counselling well. They therefore thought the counselling should have been done by neutral counsellors, from an independent AIDS NGO, for example. Finally, Act Up-Paris believed that the number of counsellors for the number of participants (one for every 80 participants) was insufficient, so there would not be adequate time for effective prevention counselling.

**Compensation, care, and treatment.** A number of international activists thought that the plan to refer participants who seroconverted during the trial to local providers and care, and the lack of assistance or care for those who were screened out because they were HIV positive, was “unethical.” In their opinion, trial participants who seroconverted should have been guaranteed access to antiretroviral therapy when they needed it. Opinions on what those who were screened out should have been offered varied. In addition, some thought that the financial “incentive” (US\$3 per monthly visit in Cameroon) was too high. They were concerned about the imbalance between the payment, which they perceived as mostly to ensure that the trial would run smoothly rather than to really benefit the participants, and the lack of treatment, which to them would have indicated a concern for the participants’ well-being over the long run.

**Access to the trial drug.** Some international activists criticised the researchers and their funders for not requiring Gilead to register tenofovir in Cameroon. They also criticised

Gilead for providing tenofovir free for the trial but not afterward;<sup>38</sup> they saw this as a particularly glaring inequity for participants who became HIV infected in the trial. In addition, they chastised Gilead for not officially accepting generic production of tenofovir, which would make it more affordable and accessible to people in all resource-poor settings, including in the countries where it was being tested.

## **Conflict and conflict resolution**

**Interactions with the researchers.** Initially, the Cameroonian researchers were open with the international and Cameroonian activists. However, after the confrontational accusations of the first meetings, the activists maintain that researchers would not meet with or respond to them. Being shut out made the activists feel that both they and their concerns had been dismissed, which they note was very destructive and “a major mistake.”

**Lack of sufficient communication among the actors.** Some activists felt that if more communication had occurred sooner among the activists, researchers, funders, and pharmaceutical representatives to discuss and sort out the issues, the results could have been different. Act Up-Paris noted that they also were not generally familiar with drug development and testing conducted or supported by not-for-profit or philanthropic organisations. When questions about the trial design and conduct arose, they did not have connections or relationships with the individuals or groups conducting the trial, or with other prevention groups with which they could raise their issues and concerns. After enrolment in the trial began in July, Act Up felt it was urgent to act and set a deadline of Christmas for the meeting being planned by UNAIDS. The meeting was not held until June of the following year.

**Response of researchers to trial suspension.** By focusing only on the government’s list of recommendations and portraying them as relatively minor issues that could be resolved, not more fundamental problems, Act Up-Paris thought that FHI ignored the larger concerns and series of events that had brought about the suspension. They thought that when FHI was trying to resolve the trial’s suspension, they worked too quickly, and still did not talk to the activists who had initiated the critique. Additionally, FHI approached local NGOs to work with them (for example, on the risk reduction counselling) without acknowledging that the trial was causing a huge controversy in the country and internationally.

37. As described on page 26, FHI maintains that they sent the French-language informed consent documents to at least two other groups in Paris that requested it; it was posted on two French AIDS websites; and Act Up-Paris never contacted FHI to request the documents.

38. Gilead had offered to provide tenofovir free for only one year to the participants who had received the placebo, if tenofovir proved to be effective for preventing or reducing the risk of HIV acquisition.



**Governmental response.** While the governmental committees did talk to the international activists, the activists also found their interest superficial, and mostly focused on the reputation and potential culpability of the Ministry of Public Health.

## Cameroonian activists

Cameroonian activists' perspectives varied by how involved they were in the process. This section presents their views, primarily those of REDS because only REDS was substantially involved throughout. Within REDS, two activists, Jean-Marie Talom and Calice Talom, were visible and vocal in protesting the trial.

### Activism

**Communication with researchers.** The local activists reported making many attempts to talk to the researchers to follow up on their concerns and demands, but say they could not get anyone to talk with them. Eventually, they were told that Professor Doh was the only person in Cameroon who could talk about the trial but that he was travelling and would not be able to see them for a month. Their inability to get the study team to respond made them feel that they were not being taken seriously and was a key factor in their continuing efforts to interrupt the trial.

**Sources of information.** Initially, their information and analysis came directly from the protocol. Later, because they could not get information directly from the researchers in Cameroon, they used their contacts in the NGO community to get more information from people directly involved in the trial, including participants and staff members. They recognised that this information was “not official” and were advised by Act Up-Paris to be careful because they could not be sure how much confidence to have in it. They did not want to cite their sources because they were concerned about jeopardizing them, so they chose to say they could not “reveal their methods for getting information.” They also had some governmental sources at the end of the controversy.

**Media.** The activists mostly worked with a journalist at *La Nouvelle Expression*, a national newspaper. When the story exploded in the media, some journalists interviewed them but others did not and just reported “whatever they pleased”—unsubstantiated hearsay and rumours.

The activists tried get the journalists to focus on the concerns they had already raised, but instead, the media spread rumours and reported things that were not true, for example, that women were being injected with HIV. They were not happy about the misinformation because they were afraid that it would discourage people from enrolling in future studies.

### Trial

REDS and Act Up-Paris had assessed the protocol together and so initially identified similar problems with the research. They included the informed consent booklets being only in English,<sup>39</sup> too few counsellors, no female condoms, an imbalance between the benefits and risks of the study, the lack of treatment for seroconverters and screen-outs, and the lack of involvement of local NGOs working with sex workers. They also later noted that there was no guarantee that participants would have access to the product if it worked. Some specifics of their point of view are:

- **Selection of researchers and financial rewards.** The Cameroonian activists perceived the relationship between FHI, CHP, and IRESCO as a closed circle that no other organisations or researchers could break into. They questioned how the same organisations and people were selected to do research repeatedly, especially given the large sums of money involved. This created an impression that the researchers were “getting rich” in the process.
- **Recruitment.** The activists said that the recruiters were paid depending on the number of women they recruited. Therefore, while some of the women were well-informed, they asserted that in some cases, the recruiters told the women what to say to fulfil the enrolment criteria. They also maintained that some of the women enrolled in the trial were “not prostitutes,” reflecting the misunderstanding that developed about the trial population.<sup>40</sup> This led them to report that when the trial became a media sensation, some of the women in the trial “suddenly heard that they were ‘sex workers’ and they were surprised because they did not consider themselves to be sex workers.” They also claimed that the trial had enrolled students<sup>41</sup> and minors. While there was no evidence presented for this claim, it was particularly sensitive, as it implied there was child prostitution.

39. As described above, Act Up-Paris and REDS continue to maintain that the informed consent was available only in English. FHI indicates that it did not receive any direct requests for the French translation from Act Up-Paris or REDS, but sent it to others when asked (SIDACTION, another activist group in Paris, and a reporter from *Le Monde*). FHI also indicates that Act Up-Paris was copied on some of this correspondence, and the French translation also was available in French on two French AIDS websites.

40. The population being recruited was high-risk women having an average of three or more coital acts per week and four or more sexual partners per month; this would include, but not be limited to, women who identified themselves as sex workers.

41. It is not clear why this would be a concern, as long as the “students” were not minors and met other criteria for enrolment.

- **Benefits/compensation.** This was the main point on which the Cameroonian and international activists' initial analysis diverged. International activists were concerned that the compensation of US\$3 per visit was too high, and hence, potentially coercive, while Cameroonians thought that it was far too low, even "derisory." One thought that because of the need to eat before taking the pill, trial participants should receive sufficient money to buy a sandwich daily. One thought that the researchers portrayed the STI, pregnancy, and liver and kidney function tests as benefits to the participants, whereas to him, these tests benefited the research rather than the women in the trial. Above all, they thought that the compensation and benefits should have been negotiated.
- **Quality of the counselling.** The activists were informed by government sources that during the first seven months of the trial, 827 STIs were identified among the 400 participants. They interpreted this to mean that the safer sex counselling was not high quality. However, they did not clarify how many of these infections were identified at the initial screening and how many occurred during the trial. According to FHI, among the 400 women enrolled in the trial, there were 11 cases of STIs among 11 women: four cases of chlamydia, three cases of bacterial vaginosis, and four cases of trichomoniasis. In addition, there were 32 cases of candidiasis among 28 women. There were no cases of gonorrhoea or syphilis detected during the course of the trial. FHI notes that they tested the women for STIs during follow-up visits only if it was clinically indicated. One activist asserted that there were 50 seroconversions during the trial, while the researchers reported that eight women seroconverted while using tenofovir across all three sites in West Africa (four in Cameroon, three in Ghana, and one in Nigeria). In addition, six more HIV infections are estimated to have occurred in the three to six months after the product was withdrawn in Cameroon.
- **Female condoms.** Contrary to what the researchers said, some Cameroonian activists maintained that female condoms were available in the country at the time and should have been included in the prevention package.
- **Follow-up treatment.** The activists' understanding was that trial participants would not receive care if they experienced problems from taking tenofovir. They shared Act Up-Paris' concern that participants who

seroconverted would not be guaranteed antiretroviral therapy. They also thought that simply referring participants who were screened out for care was not sufficient and that the researchers should at least pay for their tests.

- **Community consultation and involvement.** Cameroonian activists felt that civil society and some health authorities were not sufficiently informed about the research. These expectations were based at least partly on previous work with trials sponsored by ANRS. They stated that ANRS is required to submit the protocol to civil society actors before it is submitted for ethical review. (In fact, the ANRS Charter of Ethics for Research in Developing Countries specifies that researchers consult qualified representatives from the community and from associations of HIV-positive people about the informed consent booklet [or form] prior to submitting it to competent ethics authorities.<sup>42</sup>) While acknowledging that civil society needs to be educated about research, they believe that civil society also has a contribution to make. In their opinion, donors must insist that activists and other civil society actors are consulted.

### Efforts to restart trial product

After the trial was suspended, some NGOs were surprised that without having a meeting with the NGOs to explain the trial and discuss how to work together, FHI asked them to contract with the trial.<sup>43</sup>

Overall, REDS activists think that the tenofovir controversy advanced their cause: it generated greater interest in research and more understanding of the stakes, and increased the likelihood of partnerships and better communication. They are, however, concerned that, given the very public controversy, people may be less likely to participate in research now, and research groups may be less likely to develop research programmes in Cameroon.

### Government officials

The perspectives of government officials interviewed on why the trial was suspended and the study product never restarted were widely divergent and contradictory. Some interviewees even contradicted findings of investigative committees of which they

42. ANRS requires researchers to consult three different bodies: the ANRS Scientific Committee (consisting of multi-disciplinary experts and associate representatives from Southern and Northern countries); the country's national board of ethics; and an independent committee established for each biomedical research project (which includes qualified representatives from Southern and Northern countries). However, the charter does not mention consultation with community groups specifically apart from the informed consent booklet.

43. As noted above, FHI was exploring potential partners to which to contract the risk reduction counselling as outlined by the government audit committee. However, in the climate at the time and given the absence of any relationship, this was viewed with suspicion by many of the NGOs and activists.

themselves were members. It was not possible to determine to what extent they were saying what they actually believed versus continuing to try to deflect possible responsibility for what happened. Some government officials felt constrained in what they could say, whereas others were more forthcoming. Some put the blame squarely on the researchers, whereas others stated that it was not the research, but the media and the political fallout it generated, that brought down the trial.

### **Cameroonian and international regulations**

Certain allegations made by government officials appear to be unfounded. For example, one person claimed that the researchers had only “obtained [the government’s] agreement in principle. They were supposed to go back to the Ministry when they had their protocols approved and get an official approval. However, they started the research without doing so” and that they were “supposed to keep the Ministry informed throughout, but they did not have any further contact with the Ministry.” The administrative approval letter from the minister of health, however, only says “The Minister of Public Health hereby authorises the Family Health International (FHI) to carry out a Phase 2 study to evaluate the safety and effectiveness of the antiretroviral Tenofovir disoproxil fumarate (TDF) as a preventive method to reduce the risk of HIV infection in sexually active adults regularly exposed to the virus” and “Results generated from the present study must be presented to the legal authorities by FHI.” There is no indication of the approval being provisional or of regular updates to the Ministry of Public Health being required.

Several officials were of the opinion that the researchers “appeared to have seen the agreement with the state as a formality” and that “people think that African procedures are not valid or important.” Yet it is not clear which Cameroonian procedures and regulations the researchers are alleged to have violated. Indeed, officials also reported that Cameroonian regulations have since been revised and are now “proper,” implying that they were not adequate at the time of the tenofovir trial.

### **Ethical concerns**

Government officials were inconsistent on the issue of whether or not the research was ethical. When interviewed, some officials who were part of the initial audit commission emphasised that they had not found ethical problems, while others claimed that the trial had been unethical. However, when asked, these officials were not able to cite any specific ethical violations. The

second Medical Council Commission reported that it had “identified ethical deficiencies and dysfunctions” but gave no specific information in its public statements. While the report was never made public, people who have read it said that it stated there could be ethical issues related to several areas: combining the assessment of safety with efficacy; providing care for trial participants who might suffer health effects from tenofovir over the medium to long term; and treatment arrangements for seroconverters.

### **Community preparation and Cameroonian involvement**

Several officials thought that the study population, people with HIV, the community at large, the government, activists, journalists, and even the Cameroonian researchers were not adequately involved in the research. In particular, they thought the contact with the community was done hurriedly and that there was no public education. One official thought that there was some uncertainty about who was ultimately responsible for the trial, and noted that the Cameroonian researchers did not seem to see themselves as really being in charge of the trial, but rather that FHI was responsible and the only entity knowledgeable about all aspects of the research.

### **Communication**

Most government officials mentioned that communication problems “on all fronts” were a major contributing factor to the demise of the trial. This included communication between and among researchers from the global North and South, the activists, the study population, the government, and the public at large. They noted that the researchers did not proactively manage information and asserted that the researchers were not monitoring or paying attention to signs and therefore did not respond to the changing situation. Particularly important, the media were not informed or up to date on research in general or on many aspects of this trial in particular, so they made all kinds of assertions without real evidence or a nuanced understanding of the issues.

### **Meeting requirements to restart the trial**

One government official alleged that FHI had not rectified the first and ninth points in the “List of recommendations to be followed for the tenofovir trial suspension to be lifted” (those points being that the research should be done in an authorised health centre and that FHI and Gilead should “decide on the availability and accessibility of tenofovir for African

countries” after the trial), whereas the researchers believed they had met all requirements.<sup>44</sup> Given that the last point was vague, there may have been different views on what fulfilling it meant.

### **National reputation and government responsibility**

One official flatly stated that the trial was stopped because it had become destructive to the Cameroonian image. In particular, there was great concern that the reputation of Cameroon had been tarnished by the France 2 report. It also was noted that the Ministry of Public Health had not done what it should have. For instance, it approved the research before the ethics committee approval was received, which was irregular, according to the interviewee.

### **Trial participants**

In all of the reports, discussions, presentations, and consultations on the tenofovir trial in Cameroon, almost nothing was heard directly from the participants. Nearly all information that has circulated about their perspectives came from others—the activists, the researchers, and the media.

Cameroonian activists made a number of statements about the trial participants, such as that they had enrolled in the trial to receive health care services but were not taking the pills. It was unclear, however, where they obtained this information or how many participants the statements may have reflected.

The social science research team interviewed trial participants in Cameroon before the trial was suspended, but the full results of that research were not made available during the time of the controversies because the data were still being analysed.

The researchers reported that the participants were upset about the closure of the study. They thought participants’ feelings about the trial were demonstrated by the fact that many continued to return to the study site each month even during the suspension and despite the widespread negative associations with the study.

The France 2 programme included two women, only one of whom was actually a trial participant. In contrast to

the programme’s inflammatory allegations about the trial, the participant interviewed on the programme simply described the health care and tests that she received each month, concluding “I don’t see why this would be wrong.” The other was a young woman who provided second-hand information about a friend who was in the study who she maintained had incorrect information about the effectiveness of the pills.

The Medical Council Commission spoke with ten percent of the trial participants, but they did not provide any information about what the women had told them, except to clarify that they had not been injected with anything.

The need to keep the trial participants’ identities confidential is a major reason that more of them were not heard from directly. In addition, once the media storm began, the trial and its participants were so stigmatised that it is understandable that participants did not step forward to offer their perspectives.

### **The public**

Once the media picked up and sensationalised the tenofovir PrEP trial, it quickly became a hot topic of conversation across the country. Several interviewees reported that the “people in the street think [AIDS research] is just about money.” AIDS research does involve considerable resources, and some people can view it as corrupt and as “just eating money.”

Many people noted that the media are generally not well-informed and tend to look for sensationalism. In addition, some journalists, looking for comments, also went to people they thought would know about the trial, but who did not, and who nonetheless commented. Unfortunately, because the media were not rigorous in doing background research or checking facts, the public received a considerable amount of incorrect information about the trial. A large portion of the population generally accepted what was presented in the media and it spread. Overall, the general public appeared to have considered the government to be responsible for what happened, which is likely to have contributed to the government’s sense that they needed to act to decisively address the public’s growing alarm.

44. As previously noted, Gilead had included all African countries in its Global Access Programme, which would make tenofovir available at cost (about US\$200 per year). However, Gilead did not submit the dossier to register tenofovir in Cameroon until August 2008. They also had agreed to provide tenofovir free for one year to those trial participants given the placebo, if tenofovir was shown to be effective for preventing or reducing the likelihood of HIV acquisition.

## 4. Underlying issues and unanswered questions

### Study design and process issues

Many concerns raised about the Cameroon experience with the West African tenofovir PrEP trial stemmed from key decisions regarding study design: criteria used to determine the trial settings; the lack of existing safety data for HIV-negative women; and using formative research as the only approach to community consultation and involvement. The first two issues—study site selection and lack of safety data—were raised during the initial Gates Foundation ethics consultation in November 2001. This section explores each of these topics and their implications for the trial.

### Study site selection

Clinical trial sites have generally been identified and developed based on scientific and practical factors such as the epidemiological profile in the setting, the availability of clinical and laboratory infrastructure, local experience with research processes, and familiarity with potential collaborators. While the tenofovir trials generally followed this pattern, the selection of Cameroon and Cambodia were called into question at different times and by different groups. Additional factors were raised at the ethics consultation: the availability of antiretroviral therapy services, the potential for making tenofovir available in the country, and the appropriateness of conducting the research at the time among vulnerable groups outside the United States.

These and other concerns also surfaced during the community consultation in Cambodia, at the Bangkok conference protest, and throughout the debate in Cameroon. Favouring certain site selection factors left the tenofovir PrEP trials open to questions and criticism. For example, questions were raised about why the studies were not being conducted in the United States, and charges were made that the researchers were trying to conduct the trials inexpensively and preferred to use sex workers in developing countries as “guinea pigs.”

For any HIV prevention trial evaluating effectiveness, the study population needs to be at risk of HIV, with a high enough incidence of HIV to detect a difference in effect between the active and control groups. While trials in populations with lower risk and incidence could theoretically be done, they would require a sample size of such magnitude that they would be logistically infeasible and prohibitively expensive. In effect, they would simply never happen. Another consideration is that “high-risk” populations are in urgent need of new

prevention technologies; as such, they have an interest in the outcome of the research and could potentially benefit from the results of such trials. Since PrEP theoretically could work for both men and women, and against multiple routes of exposure (vaginal or anal sex, intravenous drug use), the range of populations potentially appropriate for PrEP trials is wider than that for some other interventions, like microbicides.

In deciding to conduct the trial in Cameroon, FHI weighted its confidence and familiarity with its Cameroonian collaborators over factors such as the lack of accessible antiretroviral therapy services at the time the trial was being planned. The protocol and public information about the trial did not sufficiently justify the choice of trial sites or contextualise the Cameroon site for the West African trial within an overall programme of PrEP research. In reality, many research collaborations are initiated based largely on previous relationships and trust.

Problems arose when the site selection was questioned based on the appropriateness of conducting a trial among high-risk women in Cameroon, where they did not have access to antiretroviral therapy and no formal organisation represented trial participants’ interests. The justification for this decision was not clear. HIV prevention trials must weigh political, ethical, and human rights criteria for site selection in addition to the traditional factors, such as scientific infrastructure, the presence of a population with adequate HIV incidence, and relationships with in-country investigators.

### “Phase”: safety versus effectiveness

Clinical trials are typically conducted in three phases. Phase 1 trials examine safety among a small number of people who are not typically at high risk of the disease in question, to ensure that the drug causes no serious harm. This is followed by a Phase 2 trial; the specific design may vary depending on the drug and indication, but generally, the trial determines the appropriate dose and assesses safety among a greater number and range of people. Finally, Phase 3 trials enrol a larger number of people who are at risk of infection to determine efficacy as well as to continue to assess safety.

The tenofovir PrEP trial was designed as a Phase 2b trial, an approach that has been used in some prevention trials to closely monitor safety while also providing an initial assessment of effectiveness. While this design included assessing safety, the trial was framed and widely perceived as an efficacy trial; the protocol

states that the trial was designed “to determine the effectiveness and safety of daily use of 300 mg tenofovir for HIV prevention.” The protocol called for analysing the safety data at six and 12 months. But by six months, the trial was already fully enrolled, so there was no clear indication that the trial would determine whether daily use of tenofovir was safe for HIV-negative people *before* proceeding to a full-scale effectiveness trial.

While the scientific community may have perceived tenofovir as generally safe based on trials among people with AIDS, no specific data existed on safety in HIV-negative women or men. The lack of this specific data left the researchers vulnerable when people asked for evidence of its safety in HIV-negative women. The researchers intended for the West Africa and Cambodia trials to carefully monitor and assess safety with clear stopping rules. Some people also questioned why a safety trial had not been conducted in the United States first. This exacerbated the perception that the trial populations were being used as “guinea pigs” and that there was a double standard. Although a protocol was developed to conduct safety trials in the United States among HIV-negative men who have sex with men, these data did not exist before the trials in Cameroon and Cambodia were to start. In any case, these data would not have assessed safety in HIV-negative women, and obviously could not address one of the main concerns, which was safety if a pregnancy occurred. While combining the safety and efficacy outcomes likely appeared to be an efficient approach to the researchers, in the end, it proved to be a false economy.

Interestingly, the West African oral tenofovir PrEP trial did provide essential safety data that some advocates had desired, and became the springboard for numerous subsequent PrEP trials.

## Community consultation and involvement

**Process for community consultation.** The tenofovir trials raise the issue of what constitutes meaningful and adequate community consultation and involvement. FHI’s decision to consider formative research as the extent of its community consultation in the Cameroon trial proved to be problematic. While formative research may have provided a systematic way to gain insight into potential participants’ views and preferences, it could not meet the broader community’s need for discussion or provide a forum for problem-solving. The lack of a community advisory board or other formal structure meant that no mechanism was in place for ongoing dialogue or conflict resolution when problems arose. In

addition, because FHI prioritised the integrity of the data and had assured confidentiality to participants in the formative research, they could not reveal who was consulted in this process, which left activists questioning the process even further.

**Who is involved?** Activists generally embrace a broader concept of “the community” than FHI pursued in the Cameroon trial. An ever wider array of national and international civil society groups now consider themselves stakeholders in the research enterprise. Advocates were surprised to learn, for example, that local and national associations of people living with HIV and AIDS did not know about the research and had not been consulted.<sup>45</sup>

Even researchers who do want to facilitate meaningful community involvement, however, find it hard to know what to do and who to approach. It also raises challenging questions about when researchers and donors can feel confident that they have sufficiently and meaningfully consulted with key actors and can move forward with a given agenda or protocol. Finally, it underscores the responsibilities of people and organisations that have been consulted to acknowledge that fact.

**Timing.** In both Cameroon and Cambodia the community outreach and consultation took place after the decision had been made to conduct the research and the protocol had been developed. The community consultation was framed as a discussion about how to do the research rather than whether and where to do it. The activists charged that organising community “consultation” or “advisory” processes after the research protocol had been developed is not meaningful. Civil society and activist organisations are increasingly calling for a greater role in defining research questions and priorities. However, current international research and funding mechanisms are not structured to operate in this way. In general, funding proposals require that specific research questions and study sites be identified up front. Devising the structure and timing of a process for community consultation is complex and risks raising expectations in communities before commitments have been made to do research. This process also will need to clarify decision-making authority among communities, researchers, donors, governments, and other review mechanisms. One positive outgrowth of the controversies in Cambodia and Cameroon, and the resulting UNAIDS consultative process, was new guidance to address many of these issues, contained in *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, developed in a consultative process spearheaded by UNAIDS and AVAC.

45. FHI notes that it did interview some people in HIV-positive groups as part of the formative research. This may mean that the activists and researchers contacted different people or that the people interviewed did not associate the formative research with the clinical trial.

## Community consultation in the Cambodia tenofovir PrEP trial

The Cambodia experience illustrates many of the same challenges that emerged in the Cameroon trial. In Cambodia, the researchers conducted formative research on a wide range of issues related to the trial and HIV/AIDS more broadly; the National Centre for HIV/AIDS, Dermatology and STI Control formed an external advisory board for the trial that met in January and June 2004 and a community advisory board (CAB) that met in March and May of 2004. While some aspects of the trial were still being determined, this was nearly a year after the initial approvals had been granted. In a thoughtful article in *The Lancet*, the researchers acknowledge that they were new to this kind of community work, and clearly HIV prevention clinical trials were new to many of the people who participated in the community advisory board. While the trial was stopped before the full terms of the community advisory board could be worked out, the researchers note that they viewed

it as a mechanism to raise and resolve a range of issues related to the trial. However, a number of people involved in the community consultation process indicated that the researchers seemed to take their questions and suggestions to mean that they did not understand important research issues. Rather than being open to adapting or modifying how the research was to be conducted, these concerns were treated more as issues that needed to be “explained” rather than addressed or changed in any way. Others suggested that some of the concerns raised in the press indicated that the research concepts were clearly foreign to some of the activists that dismissed the research by, for example, suggesting that the studies be conducted on “animals.” This underscores the need for “joint literacy” whereby both researchers and community members become more familiar with the others’ approaches, perspectives, and priorities.

**Urgency.** A broad array of people and organisations with varied perspectives noted that the process of developing and implementing the tenofovir PrEP trials moved too fast. The sense of urgency to get the trials underway was driven at least in part by the potential that tenofovir seemed to offer to provide another approach for people to protect themselves and help stop the spread of HIV. This promise and the need for new prevention approaches were especially compelling given that development of other biomedical interventions to prevent HIV—such as vaccines and microbicides—was proving to be challenging. However, this sense of urgency limited the time for community preparation, consultation, and involvement prior to the clinical trial.

**Separation of formative and clinical research.** FHI’s conscious efforts to separate the social science research from the clinical trial in the interest of objectivity meant that few outside the research team knew about the formative research or associated it with the trial. Because they did not associate the two processes, even some respondents in the formative research were not aware that they had been “consulted.” This disconnect created the impression that the researchers had made little effort to reach out to or understand the community when, in fact, the process was extensive, if limited to a research approach. In addition, not having sufficient time to analyse and disseminate the formative research results represented a real missed opportunity to highlight the careful process of inquiry as well as the content of the findings.

## Existing norms and standards

International clinical research is governed by a range of ethical guidelines and policies designed to protect participants and ensure research quality. These international standards are complemented by national and international regulatory authorities that also provide guidance on a range of issues, such as informed consent and what constitutes Good Clinical Practice. Finally, most countries also have ethical review processes for clinical research, and some have specific policies or priorities that govern research, although in practice, they are not always operational or strictly applied.

## Limitations

From a practical standpoint, however, most of these ethical guidelines have limitations. They conflict at times, and even when there is general agreement about what is and is not “ethical,” most provide general principles for research conduct rather than real operational approaches on what to do and how to do it. There is little clarity on what actions would be sufficient to satisfy the guidelines.

For example, in the area of informed consent, the guidelines may outline the elements that should be presented to potential research participants but offer little in terms of tools or approaches to actually explain complex research concepts or to assess comprehension.<sup>46</sup> This means that in many instances determining how to apply the guidelines is left to interpretation. This can result in accusations and

46. See, for example, McGrory CE, Friedland BA, Woodsong C, and MacQueen KM. *Informed Consent in HIV Prevention Trials*. New York: Population Council; 2006.

misunderstandings, as well as legitimate differences of opinion.

During the time that the tenofovir trial was being developed, there was no clear consensus among ethicists, researchers, or activists about what obligations researchers in HIV prevention trials had to provide antiretroviral therapy to trial participants who seroconverted during the trial, or those who screened out of the study because they were HIV positive.<sup>47</sup> This lack of consensus left the trial open to accusations of being “unethical,” because the larger ethical debate had not been resolved.

More recently, UNAIDS has issued guidance to clarify that trial participants who seroconvert should be ensured access to HIV care and treatment, although responsibility for fulfilling this obligation is shared by investigators, sponsors, and governments.<sup>48</sup>

Ironically, in some cases, the safeguards provided by ethical oversight mechanisms and the processes for protocol review and revision can potentially serve to undermine efforts to better meet study participants’ needs. Like all protocol changes, modifications to a study to respond to new information, needs, or norms necessitates submitting a formal protocol amendment that must be reviewed and approved by the IRBs overseeing the trial. This can create significant disincentives and even conflicts in adapting to local situations and changing contexts, especially in multi-site trials. Making any change, even in a positive direction, necessitates a long and time-consuming review process. While instituted to protect trial participants, in practice, this rigidity can stifle innovation and limit responsiveness.

### Absence of guidance

While ethics guidelines have some real limitations in terms of the areas they cover and their operational application, in some areas, there has been no guidance. Until recently, for example, there were no recognised guidelines or standards for “involving the community.” Although there is growing recognition among researchers, donors, activists, and governments that communities should play a role in research, there is little clarity or agreement about what constitutes the “community” and what role it can and should play in the clinical trial process and through what mechanism. Prompted in part by the controversies surrounding the tenofovir trials,

and following a recommendation from the UNAIDS consultation, UNAIDS and AVAC have worked with a number of other organisations to develop guidelines for Good Participatory Practice to address this gap.<sup>49</sup>

## Research management

### Responsibility and accountability

In complex, multi-site, international trials such as the West African tenofovir trial, a number of entities or groups potentially share responsibility and could be held accountable for various aspects of how the research is designed and conducted. These include the researchers and their organisations; the funders; the pharmaceutical company; the various ethics review committees; the ministries that approve a trial; and through its laws, policies, and systems, the government of the country in which the trial is being conducted. There is at present little consensus on who is primarily responsible for some crucial aspects of the research and thus who should be held accountable if something goes wrong.

For example, who is ultimately responsible for ensuring access to the drug being tested (to the trial participants and in the country in general), if it is shown to be effective: the funder, the research institution, the Ministry of Public Health, the national ethics committee, and/or the pharmaceutical company? In particular, who is responsible in a situation such as this one, in which the pharmaceutical company is not the main sponsor or initiator of the research but could benefit financially nonetheless?

When accountability is unclear or shared, as in these tenofovir trials, it easily can turn into a situation in which everyone is potentially accountable, but no one is ultimately accountable.

As a result:

- People or groups were at times held accountable for things they had not decided and did not have the power to change.
- People or groups were at times held accountable or blamed because from someone’s point of view, they should have taken more responsibility, whereas they did not see themselves as responsible.

47. See, for example: (1) Weijer C, LeBlanc GJ. The balm of Gilead: Is the provision of treatment to those who seroconvert in HIV prevention trials a matter of moral obligation or moral negotiation? *Journal of Law, Medicine & Ethics*. 2006;34:793–808. (2) UNAIDS. *Ethical Considerations in HIV Preventive Vaccine Research*. Geneva, CH: UNAIDS; 2000. (3) Bass E. Ethics, antiretrovirals and prevention trials: an online debate with Ruth Macklin and Charles Weijer. *JAVI Report*. September 2003–January 2004;7(3). (4) GCM. *Rethinking the Ethical Roadmap for Clinical Testing of Microbicides: Report of an International Consultation*. Washington, DC: GCM; 2005.

48. UNAIDS. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007.

49. UNAIDS and AVAC. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007.



- The responsibility for problems could be easily passed to others.
- Groups were at times held accountable for political or strategic reasons rather than because they were clearly responsible.
- Some people or groups were not held accountable, when perhaps they should have been.
- It was unclear who should take the lead on addressing issues raised and who should bear the financial burden.

Hence, different people and groups thought particular entities had the main responsibility for the trial conduct and the issues raised. For example:

- At different times, it appeared that the French activists thought Gilead, FHI, the Gates Foundation, and/or the Cameroonian researchers were primarily responsible for the research.
- The Cameroonian activists appeared to see the Cameroonian researchers as having primary responsibility for how the trial was designed and conducted, whereas the Cameroonian researchers saw FHI as primarily responsible.
- Many in the Ministry of Public Health viewed the Cameroonian researchers as having the main responsibility, whereas the Government of Cameroon appeared to consider the Ministry of Public Health as responsible.
- By contrast, the media and public thought the government, and to some extent the Ministry of Public Health, were accountable.

Ultimately, more consideration needs to be given to what makes a person or organisation accountable for something. What are the systems and entities that have oversight and authority to hold these entities or individuals accountable?

Situations also occurred in the Cameroon PrEP trial site in which one group felt responsible for a certain dimension, and others felt that they should not be responsible. For example, the researchers felt it was their ethical responsibility to ensure that the trial participants got the best possible prevention counselling, which to them meant they had to provide it. However, the activists felt that the researchers should not be responsible for this since they believed that there was a potential conflict of interest (see footnote 33, page 26). If the counselling is transferred to NGOs, who is then ultimately responsible for ensuring that it is high quality and effective—the researchers or the NGO?

### **Supervision and internal authority**

The trial involved many types of actors, with different roles, degrees of power, and responsibility, who were

physically located in different places. For example, in Cameroon, those directly implementing the trial were at the research site in Douala, with the coordinator and managers in Yaoundé, about three hours away by road, while ultimate oversight and responsibility rested with the principal investigators at FHI in the United States.

When difficulties arose, the factors outlined above had several effects:

- The Cameroonian researchers and trial staff made statements that reflected varying levels of clarity and understanding of the protocol itself as well as the intricacies of prevention trials.
- In addition, some changes were reportedly in process that were not yet reflected in the trial protocol or the informed consent booklets. While the researchers on the ground knew that changes were in process, they were not always clear about the process or the status of particular proposed changes. When trial documents reflected one thing and people involved with the trial said a variety of other things when questioned, it gave the impression of disarray, confusion, and obfuscation.
- The FHI staff who sought to address the problems had not been in the country as the trial unravelled and did not have a clear enough picture of what had happened or of the depth of the problems and the complexity of the situation. In retrospect, there were clear indications of problems that they failed to notice: in some cases, spotting the problem but not how serious it was, and in others, not seeing the problem at all.

### **Conflict resolution and crisis management**

Resolving divergent points of view and conflicts can be difficult in the best of situations. It is even more challenging when the main protagonists are not familiar with each other, have clashing styles, and have an instinctive distrust of each other. The following issues also made it more difficult to resolve the conflicts that arose in the tenofovir trials.

**Geographic spread, roles, and responsibilities.** The complexity of the trials' organisational structures, with multiple layers and people with varying roles and responsibilities in different places, contributed to the difficulty of resolving issues. Those on the ground had more detailed knowledge about the situation as it unfolded, but less authority to resolve issues; the international researchers, with the most authority, were the furthest from the ground. Because issues and problems tended to be taken up with the people who were at hand, the Cameroonian researchers were the most frequently approached, and became both the conduit and filter of information to the international researchers. Consequently, the

international researchers were not always fully aware of the specific events and broader climate that led to the problems and ultimate suspension. This made it more difficult for them to appreciate the level and nature of the crisis and ascertain what might lead to a resolution.

**Approach to resolution, timing, and speed.** The international researchers tried to resolve the problems without necessarily fully understanding the origins, nature, or level of the crisis. In the case of Cameroon, they did not intervene during the months when the problems were developing and may have been more easily resolved. When FHI did intervene following the suspension, it was probably already too late. At that time, FHI focused only on the government's recommendations, without going back to the activists' concerns. The activists saw this approach as trivializing their concerns, which they thought required discussion and consensus-building with the broader community.

**Processes for "adverse political events."** While all clinical trials have specific procedures in place for managing adverse clinical events, most do not have systems to detect, monitor, or respond to adverse events of a more political nature. In the case of the tenofovir trials, there were no clearly defined processes for dealing with concerns coming from people outside of the trial, such as activists. Thus, in the Cameroon trial, local researchers who met with the international and local activists had to decide on the best process for dealing with the issues raised.

In sum, this experience underscores that trials need systems to monitor for potential problems and formalised processes for handling concerns and resolving conflict.

## Communication and language

Communication was perhaps the most important factor leading to the collapse of the trials.

### Lack of communication

In Cameroon, when the activists attempted to follow up with the researchers on their initial discussion, the researchers did not respond in a timely manner. The activists felt ignored and disrespected, which generated frustration and anger, increasing their determination rather than abating it. The information vacuum created the impression that something was being hidden. More responsiveness, on the other hand, may have contributed significantly to creating a climate of respect and openness, which in turn could have made

communication more possible and fruitful. Many opportunities to communicate were missed.

### Indirect communication

Much of the communication that did occur between the activists and the researchers was indirect and one-way, through protests, web postings, publications, and press conferences or releases. Dialogue between those funding and implementing the trials and those with concerns about it could have helped resolve the issues and avert the suspension. However, despite some attempts to organise a serious dialogue, there was no such communication until after the trial was suspended.

### Style and tone

The style, tone, and framing of messages naturally affect the way in which they are received. At times, the style of communication used was intentionally inflammatory or provocative and issues seemed to be framed more for effect than for accuracy. For example, Act Up's language and tone was accusatorial and called into question the motivations and good will of the investigators. While this style is more likely to get noticed, it is also more likely to provoke those to whom the message is directed and thus hamper dialogue and issue resolution.

### Choice and precision of messages

At times, the major players expressed themselves in vague or loose terms; in a situation of conflict, precision is crucial for effective communication. Regarding using the term "unethical," for example, when asked which recognised ethical standard had been breached, sometimes the activist, journalist, or National Medical Council Audit Commission was unable to be specific.

### (Mis)Interpretations

There were many instances in which messages or actions were interpreted through the lens of an actor in ways that did not reflect the intended meaning or in some cases the reality. For example, when the French translation of the informed consent booklet was not provided to activists, they interpreted this to mean that it did not exist. The report that 827 cases of sexually transmitted infections were identified among the trial participants was taken by the activists to mean that these were identified while the women were participating in the trial. This was put forward as "evidence" that the risk reduction counselling was poor, when in fact, the vast majority of these infections were identified in the screening process, before the women were enrolled in the trial and had participated

in the risk reduction counselling. The aggressive tactics directed at Gilead by activists during the Bangkok meeting were interpreted by the researchers as their being extreme and unwilling to talk. This impression was reinforced by Act Up-Paris' statement that "we demand the immediate halt of the Tenofovir prevention trials...as they are currently being conducted," which was interpreted to mean that they wanted to shut down the trial no matter what.

### **Communication in the conflict zone**

Mistrust and potential conflict make communication more difficult. In the case of the tenofovir trials, mistrust led to diminishing transparency, which compounded the difficulties and created further mistrust. In addition, accusations or confrontations tend to generate defensiveness. There were few, if any, instances in which people publicly acknowledged that another point of view was legitimate, regardless of whether or not they agreed. Accusations also got in the way of all parties stating clearly what had been done and why, admitting mistakes, and acknowledging that they could do better.

### **The role of the mass media**

The media played a significant role in the breakdown of the tenofovir trials in both Cameroon and Cambodia, albeit in somewhat different ways.

In both settings, the media carried the conflict into the public arena, amplifying many of the communication problems described above. They helped to draw attention to the trials and issues, both nationally and internationally, but also contributed significantly to spreading and even generating misinformation. For example, in Cameroon, the France 2 programme, which was neither balanced nor well-researched, marked the start of closer media and public attention to the trial. The story was then picked up in the national press in Cameroon, and a number of the distortions from the France 2 programme were magnified in the coverage. The Cameroonian public tends to believe the Cameroonian media despite the fact that basic journalistic principles, such as integrity, objectivity, source and fact-checking, and verification from multiple sources are relatively weakly applied, if at all. This contributed to growing public concern that took on an air of hysteria, and effectively, it became impossible to have a more rational discussion of the trial and how to address the concerns. In addition, it put people on the record, forcing government officials in particular to take public positions.

## **Activism**

Activists raised important issues regarding the tenofovir trials specifically and prevention trials generally. They ultimately played the catalytic role in the outcome of the trials in Cambodia and Cameroon, demonstrating that civil society organisations, including activists, have a stake in trials and researchers need to involve them from the outset. The part they played in the tenofovir trials also highlights some important issues about activist roles and responsibilities.

### **Strategies and their impact**

Activists concerned about the Cameroon trial site made decisions on strategy based on their perceived potential for drawing attention rather than on how effectively or accurately the strategy would carry their message or how they would be perceived. Strategies appeared to be decided on in reaction to a given situation, rather than forming part of a planned set of actions with clear goals and possibly escalating steps to achieve them. For example, rather than presenting their issues in writing to CHP and FHI first, and putting them on the Internet or elsewhere only if they did not respond, Act Up-Paris and REDS issued them right away in a press release, posted on the Act Up-Paris website.

At times, these decisions, rather than advancing their cause, created negative or dismissive reactions in those they sought to reach. For example, the activists focused on Gilead (as "big pharma") because it would draw more attention to the issue, although they knew that Gilead was not sponsoring or conducting the trials. Tactics such as throwing fake blood on the booth at the AIDS conference in Bangkok caused some people to think that the activists were ill-informed and extreme. The corollary harm was that the activists' legitimate points and concerns got lost.

Raising issues in such provocative ways, while a signature of groups like Act Up-Paris, affected the potential for trust, communication, and relationships to develop. These methods gave the researchers the impression that the activists wanted to stop the trials at any cost, which Act Up-Paris later said was not their intention. They cast doubt on the activists' interest in dialogue to resolve problems or in seeing new prevention technologies tested in general.

### **Standards of evidence**

Activists were inconsistent in the standards of evidence they upheld for their claims. At times, assertions were made based on little real evidence. For example, the claim that the informed consent booklets were not in

French when the trial began—which is still repeated—was based on the fact that the activists were not given the French booklet at the time they were given the English one.

While some additional activists joined in to oppose the trial, others were more cautious, and some disagreed with the approaches and outcome outright. Like other varied groups, not all advocates or activists use or approve of the same strategies or share the same political philosophy. One commented on a listserv that the accusations were very serious if true, but that more documentation was needed. The groups most closely involved in the Cameroon trial, like Act Up-Paris, tend to be more radical and more likely to use “street protest” and hyperbole than most advocates. Nonetheless, more than a year after the trial was suspended, some activists continued to repeat statements for which there was no concrete evidence.

### **Mutual transparency**

Activists expected the researchers to be transparent about their methods, intentions, and documents. However, they were sometimes unwilling to be as transparent about their own claims, particularly at the international meetings after the trial closures. In these instances, they declined to state the sources of their information. This meant that researchers and others

did not know whether the accusations were based on direct information from credible sources, or whether they were based on information from one or two trial participants or from a much larger number. This made it difficult to put the claims into perspective or assess their seriousness. If the claims were based on anecdotal evidence, openness and clarity about this would have strengthened the activists’ position.

### **Oversight and accountability**

Activists generally consider themselves accountable to their mission, principles, and in some cases, a constituency. Many of the researchers, donors, and others involved in the tenofovir PrEP trials expressed concern that there are no real enforceable mechanisms for holding activists accountable. This means that activists could make unfounded statements or “unreasonable” demands without being accountable for the consequences. These consequences could be substantial: wasting enormous resources, discouraging donors and scientists, and ultimately derailing testing and development of new prevention technologies. Aside from a concern for their own reputations and credibility, including the degree of involvement and influence over the long term, enforceable mechanisms for such accountability are unclear.

## 5. Requirements for future prevention trials

The Cameroon experience with the tenofovir trials raised HIV prevention research to a new level, with increased visibility, accountability, complexity, and cost. The experience made clear that biomedical

research is an increasingly political process, and that controversy in the community or media can undermine a trial as surely as scientific setbacks. Conducting a trial “under the radar,” whether or not that is appropriate, is simply no longer an option. Trial sponsors, funders, researchers, activists, and governments all need to understand, appreciate, and respond to this changed context.

Below we outline a series of requirements that are essential to the effective implementation of HIV prevention trials. If we are to prevent future “prevention trial failures,” these must be the new normative standards.

For the most part, these measures will not surprise most readers. Several of the ideas have surfaced in other forums, including some of the other consultations, articles, and reports that have resulted from the tenofovir controversy. Civil society groups—like GCM and AVAC—are working to develop and test practical approaches for addressing key issues such as community consultation, providing treatment for seroconverters, and expanding research literacy. Similarly, as research has moved forward, a number of research organisations—including FHI—have made important strides toward adapting their research approach to this new reality, including engaging a wider array of stakeholders earlier in the process, and better preparing investigators to anticipate and respond to communication challenges.

### Study design and process

- Research protocols or other formal trial-related documents must include a clear rationale for selecting the trial site and trial population. Such documents can be important communication tools and ultimately can serve to protect the trial and the researchers. Researchers and advocates should put together a joint process to develop guidelines for site selection that consider social and political factors as well as scientific ones.
- Researchers should include national and community stakeholders in the protocol development phase, and ask for critical input during the design of the trial when changes can still be made. Consulting with civil society after a protocol is completed is little more than cosmetic, and will be perceived as such.
- The urgency of HIV prevention research—as compelling as that may be—needs to be continually balanced by the false economy of proceeding too quickly. HIV prevention trials demand substantial and prolonged engagement with the community and national stakeholders prior to the initiation of a trial.
- Outreach efforts must go beyond the trial’s immediate geographic setting and include provincial, national, and possibly international stakeholders.
- While important, formative research should not substitute for an open process of consultation that is recognised as linked to a trial and influences that trial.
- Trial processes should include an explicit “conflict resolution” plan and consider designating a community ombudsperson who can receive and elevate concerns, facilitate communication, and ensure that questions and concerns are responded to in a timely manner.

### Research culture

- Social science research and researchers must be accorded higher status within the structure of clinical trials, including shared authority in decision-making around protocol design. This is especially important in trials evaluating user-controlled interventions such as PrEP or microbicides because behavioural components are critical to the trial conduct and analysis.
- Country-level researchers should be more centrally involved in designing trials as well as implementing them. This will allow the trial to draw on their knowledge of local realities and help rectify the historic power imbalance between Northern and Southern researchers.

### Norms and standards

- Researchers, advocates, and governments must forge a shared framework of expectations, accepted norms, and practical approaches to community involvement. The Good Participatory Practice guidelines developed by UNAIDS and AVAC are a good first step in this direction. Efforts to determine whether these guidelines can be made normative for HIV prevention trials should continue.

- International ethics bodies and researchers should develop guidelines specific to HIV prevention trials, such as standard of care for trial participants, approaches to risk reduction counselling, and the burden of proof of safety data needed to progress to efficacy testing. Important progress in this regard has been made with the publication by UNAIDS of *Ethical Considerations in Biomedical HIV Prevention Trials*.
- Operational guidance is needed on treatment and long-term care for individuals who seroconvert during clinical trials. The Global Campaign for Microbicides is currently working with partners to develop an international trust fund and insurance scheme to address this issue, and in 2008, FHI published *Partnering for Care in HIV Prevention Trials: A How-To Manual*.<sup>50</sup>
- Governments must develop and enforce clear national guidelines on issues such as participant remuneration, standard of care for trial participants and those screened out, community participation and other consultative processes, and post-trial access to products.

## Research management

- Research networks and partnerships must anticipate and plan for “adverse political events” as routinely and concretely as they do now for adverse clinical events. This includes proactive communications planning and investment in mechanisms to build relationships with respected local stakeholders. Important progress in this regard has been made via the creation of communities of practice such as the Microbicides Media and Communications Initiative.<sup>51</sup> The field of PrEP research now includes a PrEP working group of investigators, as well as a PrEP communications group.<sup>52</sup>
- Onsite researchers and staff need to develop communication skills, as well as in-depth understanding of the rationale, design, and implementation approaches of the trial. Trial documents need to clearly articulate which entities and individuals are ultimately responsible for what aspects of the trial.
- Trials need specified processes and mechanisms for handling questions, enquiries, and complaints—ideally, a highly informed neutral actor well-armed with facts, documentation, and access; for example,

a community advisory board, ombudsperson, or community liaison.

- Provisions must be made for post-trial access to products and interventions by trial participants, communities, and host countries; for example, setting preferential pricing, registering the drug in the host country, and what actors are responsible for delivering and following up on what.

## Communication and language

- Skilled communications professionals as well as the researchers themselves should actively reach out to the national and international media, medical professionals, and civil society on the rationale, plans, and progress of trials.
- Challenges, difficulties, and setbacks should be dealt with in an honest and straightforward way. Responsiveness and respect should infuse all communication.

## Advocacy and activism

- Advocates should work toward devising clear goals and using strategies that correspond with those goals. Certain strategy choices, such as going to the press or staging public protests, are effective tools that have led to many important scientific, health, and human rights gains. However, such strategies can be difficult to control, and may have significant unintended consequences.
- Advocates need to judge themselves and each other by the accuracy of their facts, not just their moral passion and conviction that they are on “the right side.” Advocates as well as researchers should be held accountable to standards of evidence and responsible behaviour.
- Advocates should caution themselves and each other against overstated claims to represent constituencies such as “the community” or “women” or “sex workers” without a clear basis for such assertions.

## Looking ahead

The lessons from the tenofovir PrEP trial site in Cameroon were hard won and costly. The

50. MacQueen KM, May M. *Partnering for Care in HIV Prevention Trials: A How-To Manual*. Research Triangle Park, NC: Family Health International; 2008.

51. The Microbicides Media and Communications Initiative is a group that includes advocates, scientists, and communications experts from all of the institutions currently sponsoring microbicide trials. It meets regularly in person and by conference call to share strategies across trials and anticipate and respond to the special communications challenges posed by large-scale effectiveness trials.

52. The PrEP working group is coordinated by the Forum for Collaborative HIV Research ([www.hivforum.org/](http://www.hivforum.org/)) and the PrEP communications group is coordinated by AVAC ([www.avac.org/](http://www.avac.org/)).

controversies laid bare the sometimes fragile underpinnings of relations among the numerous constituencies involved in clinical trials for HIV prevention: researchers, trial participants, activists, governments, donors, journalists, normative agencies, and others. This experience also demonstrated the different meanings and expectations that groups and individuals attach to issues that are central to trials, such as community, participation, and ethics. It underscored that despite a shared commitment to addressing the ravages of the AIDS epidemic, misunderstandings and mistrust continue, particularly given sometimes stark disparities of wealth and access to health innovations, knowledge, and other resources.

Yet the controversies surrounding the early tenofovir PrEP trials also forced the prevention research field to reflect on its work in a way that helped usher in and accelerate efforts to develop and define new approaches to HIV prevention research characterised by greater transparency, inclusiveness, and consultation. These efforts are ongoing, and they remain far from perfect. Many lessons are still being learned—and will continue to be learned—as these approaches are adapted to new settings and new science. But there is growing attention to making consultation and participation more central and systematic elements of the trial process, as demonstrated by new work to develop guidance, foster innovation, and conduct evaluation.

Finally, despite the challenges from the Cameroon and Cambodia experiences, trials to identify effective agents for pre-exposure prophylaxis have continued and accelerated. Trials testing tenofovir and Truvada (a combination drug including tenofovir and FTC) for PrEP for HIV prevention are underway and being planned in Africa, Asia, Latin America, and North America. If these trials proceed as planned, by the middle of 2009, some 20,000 people worldwide will be enrolled in PrEP trials. These trial participants reflect the diverse populations most affected by the AIDS epidemic—serodiscordant couples, men who have sex with men, injecting drug users, and high-risk women. Researchers and communities in many of these trial settings are working to build on the lessons from Cameroon in an effort to do better—better and more relevant research, better consultation, and better communication. Activists are working with normative agencies, researchers, and governments to prepare for conveying the trial results to diverse constituencies, and to develop clear plans for accelerating access if the trial results are positive. This work demonstrates the continuing evolution of the HIV prevention research field, of which the experience with the Cameroon tenofovir PrEP site represents an important if difficult chapter.

## Annex 1. Timeline of Family Health International’s West Africa oral tenofovir PrEP trial in Cameroon

	<b>Sept 8:</b> Gilead Sciences visits Family Health International (FHI) to discuss role of tenofovir in HIV prevention research
2	<b>Oct 6:</b> FHI and Gilead visit the Bill & Melinda Gates Foundation to discuss their interest in funding a tenofovir pre-exposure prophylaxis (PrEP) trial
0	
0	<b>Oct 26:</b> US Food and Drug Administration approves tenofovir for treating people with AIDS
1	
	<b>Nov 27:</b> Gates Foundation holds ethical consultation on FHI proposal to test oral tenofovir in a Phase 3 trial in Cameroon
2	<b>Oct 28:</b> Gates Foundation approves US\$6.5 million grant for multi-national trials to evaluate the safety and efficacy of tenofovir for reducing the risk of HIV infection in high-risk sexually active adults
0	
0	<b>Dec:</b> Gilead announces its Global Access Programme to make tenofovir available, if effective, at nonprofit cost in 68 developing countries
2	
	<b>Jan 23:</b> Minister of Public Health authorises FHI to conduct the trial of oral tenofovir in Cameroon
0	
0	<b>Sept:</b> Formative research begins in Douala
3	
	<b>Dec 16:</b> National Ethics Committee of Cameroon clears the study protocol through December 15, 2004
	<b>Apr 22:</b> Littoral Provincial Delegation of the Ministry of Public Health authorises the study to be conducted in Douala
	<b>May–June:</b> Act Up-Paris and Réseau Ethique Droit et Santé (REDS) research trials in Cameroon for second issue of <i>Protocol Sud</i>
	<b>July:</b> Trial begins enrollment
	<b>July 11–16:</b> XV International AIDS Conference is held in Bangkok
	<b>July 12:</b> AIDES issues statement calling for antiretroviral therapy for trial screen-outs and participants who seroconvert
	<b>July 14:</b> Act Up-Paris, Women’s Network for Unity, and the Asian Pacific Network of Sex Workers take over Gilead’s symposium at the Bangkok AIDS conference
2	
0	<b>July 16:</b> Act Up-Paris and the Asian Pacific Network of Sex Workers publishes press release denouncing the tenofovir trials
0	
4	<b>Sept 29:</b> Conference call takes place among AIDS, sex worker, and microbicides nongovernmental organisation activists and advocates to talk through their issues with the tenofovir PrEP trials
	<b>Oct 25:</b> Conference call takes place among donors, researchers, and activists about the issues with the tenofovir PrEP trials
	<b>Dec 1:</b> <i>La Nouvelle Expression</i> publishes article written by REDS on the trial
	<b>Dec 11:</b> National Ethics Committee of Cameroon extends its ethical clearance for the study until December 15, 2005
	<b>Dec:</b> Cameroon site of West African tenofovir PrEP trial is fully enrolled



2 0 0 5	<b>Jan 17:</b> France 2 airs its report on the tenofovir trial site in Cameroon
	<b>Jan 20:</b> Members of Act Up-Paris demonstrate in the Cameroon embassy in Paris
	<b>Jan 23:</b> Minister of Public Health commissions “audit” of trial in response to allegations made in the France 2 report
	<b>Jan 24:</b> Minister of Public Health defends the trial to the press
	<b>Jan 27:</b> FHI issues a press release about the trial and the France 2 report
	<b>Feb:</b> Intense flurry of news reports on the trial in Cameroon generates public concern
	<b>Feb 3:</b> Minister of Public Health notes “dysfunctions” in audit report but no ethical violations, and temporarily suspends the trial
	<b>Feb 7:</b> Cameroon National Medical Council (CNMC) sets up its independent ad hoc commission of inquiry under direction of Professor Tetanye Ekoe
	<b>Feb 7–15:</b> Ward Cates, President of FHI, visits Cameroon
	<b>Feb 14:</b> Ministry of Public Health agrees to follow-up of study participants whilst FHI works to comply with recommendations (but no drug is given)
	<b>Feb 23:</b> President of the CNMC, Dr. Daniel Muna, holds press conference on the findings of the ad hoc commission and asserts that ethical norms were violated, along with other ethical deficiencies and dysfunctions, but gives no details
	<b>Mar:</b> Gilead expands its Global Access Programme to 97 developing countries
	<b>May 19–20:</b> International AIDS Society stakeholder consultation is held to address issues related to tenofovir prophylactic research
	<b>March–June:</b> Joint United Nations Programme on HIV/AIDS (UNAIDS) regional stakeholder meetings are held on “Creating Effective Partnerships for HIV Prevention Trials” (Abuja, Nigeria; Durban, South Africa; Pattaya, Thailand)
	<b>Jun:</b> UNAIDS international stakeholders meeting is held on “Creating Effective Partnerships for HIV Prevention Trials” (Geneva, Switzerland)
<b>Aug:</b> Final follow-up visit for trial participants takes place	
<b>Dec 13–14:</b> PrEP HIV Prevention Stakeholder Consultation and Action Plan Meeting is held in Yaoundé	
2 0 0 6	<b>Aug:</b> Presentation is made of trial results at the XVI International AIDS Conference in Toronto
	<b>May:</b> Trial results are published: Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a Phase 2, double-blind, randomised, placebo-controlled trial. <i>PLoS Clin Trials</i> . 2007;2:e27
2 0 0 7	

## Annex 2. People interviewed for the Cameroon tenofovir pre-exposure prophylaxis trial case study

Ward Cates, President, Family Health International

Anderson Sama Doh, Coordinating Investigator, University of Yaoundé, Faculty of Medicine

Hugues Fischer, Act Up-Paris

Laurence Gaubert, Médecins Sans Frontières Cameroon

Gregg Gonsalves, Gay Men's Health Crisis

Yasmin Halima, International AIDS Society

Cate Hankins, Joint United Nations Programme on HIV/AIDS

John Kaldor, University of New South Wales

James Clovis Kayo, ReCAP+ (Réseau Camerounais des Associations de PVVIH)

Sinata Koulla-Shira, Ministry of Public Health

Alexis Boupda Kuate, Care and Health Programme

Pierre Ongolo Logo, Ministry of Public Health

Kate MacQueen, Family Health International

Vivian McLaurin, Family Health International

Henriette Meilo, Principal Investigator

Sanushka Mudliar, former staff, Oxfam Cambodia, Consultant

Peter Ndumbe, University of Yaoundé, Faculty of Medicine, member of audit commission

Falimatou Ngampoua, Care and Health Programme

Tiburce Nyiama, Institute de Recherches et des Etudes de Comportements

Essame Oyono, Ministry of Research

Leigh Peterson, Family Health International

Supriya Pillai, former staff, Population Services International Cambodia

Fabrice Pilorgé, Act Up-Paris

Marie-Thérèse Rannou, Service de Médecine, Hôpital Bicêtre, Hôpitaux de Paris

Renee Ridzon, Bill & Melinda Gates Foundation

Beth Robinson, Family Health International

Kimberly Page Shafer, University of California at San Francisco

Dawn Smith, US Centers for Disease Control and Prevention, Botswana pre-exposure prophylaxis trial

Markus Steiner, Family Health International

Calice Talom, Réseau Ethique Droit et Santé

Jean-Marie Talom, Réseau Ethique Droit et Santé

Roger Teck, Médecins Sans Frontières Cameroon

Gaye Tharawan, Consultant, Global Campaign for Microbicides

Emmanuel Trenado, AIDES

Mitchell Warren, AIDS Vaccine Advocacy Coalition

## **Annex 3. Participants, Bill & Melinda Gates Foundation Tenofovir Trial Ethics Consultation, November 27, 2001**

Helene Gayle, Gates Foundation

Ward Cates, Family Health International

Ronald Roddy, Family Health International

Kate MacQueen, Family Health International

Zeda Rosenberg, Family Health International

James Rooney, Gilead Sciences

Greg Alton, Gilead Sciences

Angela Wassuna, The Hastings Center

Lori Heise, Global Campaign for Microbicides

Ruth Faden, The Johns Hopkins University, Berman Institute of Bioethics

James Curran, Emory University, Rollins School of Public Health

Lynn Paxton, US Centers for Disease Control and Prevention, National Center for HIV, STD, and TB Prevention

Salim Abdool Karim, University of Natal, South Africa

## Annex 4. Additional resources

AIDS Vaccine Advocacy Coalition (AVAC). *Will a Pill a Day Prevent HIV? Anticipating the Results of the Tenofovir PREP Trials*. New York, NY: AVAC; 2005. Available at [www.avac.org/prep08.pdf](http://www.avac.org/prep08.pdf). Accessed January 5, 2009.

Collins C. *Gaps and inconsistencies in ethical guidance for HIV prevention research*. Background paper prepared for the Joint United Nations Programme on HIV/AIDS (UNAIDS). Geneva, CH: UNAIDS; 2005.

Joint United Nations Programme on HIV/AIDS. *Ethical Considerations in Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at [data.unaids.org/pub/Manual/2007/jc1349\\_ethics\\_2\\_11\\_07\\_en.pdf](http://data.unaids.org/pub/Manual/2007/jc1349_ethics_2_11_07_en.pdf). Accessed January 5, 2009.

Heise L, Shapiro K, Slevin K. *Mapping the Standards of Care at Microbicide Clinical Trial Sites*. Washington, DC: Global Campaign for Microbicides; 2008.

Joint United Nations Programme on HIV/AIDS and AIDS Vaccine Advocacy Coalition. *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*. Geneva, CH: UNAIDS; 2007. Available at [data.unaids.org/pub/Manual/2007/jc1364\\_good\\_participatory\\_guidelines\\_en.pdf](http://data.unaids.org/pub/Manual/2007/jc1364_good_participatory_guidelines_en.pdf). Accessed January 5, 2009.



In the laboratory perhaps, science can indulge its natural preferences for objectivity, political neutrality, and pristine research environments. But in the field of HIV prevention research, with its numerous sensitivities, that expectation is naïve and can invite failure. Researchers need to fully internalise that insufficient attention to political context, ethical issues, and public perception can halt a clinical trial as definitively and quickly as negative findings at a data safety and monitoring board review.

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